

## CLINICAL REVIEW

NDA-21368

crossover study was conducted to investigate the pharmacodynamic interaction between alcohol (0.6 g/kg) and tadalafil (20 mg), administered as single oral doses, and to further evaluate the safety and tolerability of tadalafil administered as a single 20 mg oral dose. Forty-eight (48) male subjects were randomized to receive either 20 mg tadalafil or placebo in each treatment period. Approximately 2 hours after administration of tadalafil or placebo, subjects received a dose of alcohol (0.6 g/kg). Supine and standing blood pressure and heart rate measurements were performed at regular intervals up to 24 hours post-tadalafil or placebo dose as an assessment of a potential pharmacodynamic interaction.

The notable findings in 20 mg study were as follows:

- According to the sponsor, the incidence of clinically significant reductions in both supine and standing systolic and diastolic BP was similar following administration of 20 mg tadalafil or placebo with alcohol.
- For pharmacodynamic endpoint (maximum reduction in standing systolic blood pressure) the 95% CI for the mean difference between the two treatments was contained within the predefined equivalence limits of -8 to +8 mmHg.

### Medical Officers comments:

1. In the first study with 10 mg IC351 dose and alcohol, the maximum hypotensive effect was seen at 4 hours and by 10 hours the parameters had returned to base line. The clinical significance of diastolic blood pressure drop in 3 patients in this study was unclear and needs to be looked at in context of the larger data base of clinical trials and the studies with 20 mg dose. It is well known that the consumption of this much alcohol will impair some of the CNS parameters however because of its vasodilatory properties one has to be careful about additive effect of IC351.

2. In the second study, 20mg IC351 and alcohol showed little difference between the treated and placebo groups.

### 5.2.3 Pharmacometric studies:

Population analyses were conducted in over 950 patients in three Phase 2 studies (LVAC, LVBF and LVBG), and in one Phase 3 trial (CSR.LVCE). Response scores to IIEF Question 3 and Question 4 were used as endpoints in PK/PD analysis all four studies. These questions measured the ability to penetrate and to maintain an erection during an intercourse. The scores were regarded as categorical response variables. These studies showed that for vast number of patients 10 mg got the highest effect. And in one study LVBF, *the sponsor concluded that all the probabilities plateau at approximately 10 mg, therefore giving doses above this do not achieve higher dynamic effect.*

### Medical officer's comment:

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Cialis™ has a median  $c_{max}$  of 2 hours and  $t_{1/2}$  elimination of 17.5 hours. The Pharmacometric studies further confirm this reviewer opinion based on sponsors pivotal efficacy studies that a 10 mg should be the starting dose in otherwise healthy and 5mg in renally compromised patients.

A large number of patients suffer from mild to moderate form of ED, that can use 5 mg OR 10 mg as a starting dose.

### 5.2.4 Effects of Intrinsic and Extrinsic Factors

#### Age and Gender

Plasma concentrations of IC351 in 12 healthy elderly subjects (aged 65 to 78 years) were 25% greater than values in 12 healthy young subjects (aged 19 to 45 years), indicating a slight reduction in oral clearance with age (LVBW). Given the PK/PD properties of this drug, a dose adjustment may be required.

In female subjects, steady-state IC351 concentrations were slightly (13%) higher than in male subjects (CSR LVAD). This small gender effect was considered to be of no clinical significance. Both genders could be enrolled in clinical pharmacology studies and results were generally not differentiated by gender.

#### Ethnic Origin

The effects of ethnic origin on IC351 disposition have not yet been characterized. Majority of the patients in the phase 3 primary controlled studies conducted were Caucasians (79.8%). Asians constituted about 16% and hispanics 2.6%. African americans contributed <1% (n=12) to the pivotal study population. According to the sponsor a study is currently ongoing to compare IC351 pharmacokinetics in Japanese and Caucasian subjects (LVCS).

#### Diabetes

Systemic exposure to IC351 in subjects with diabetes was 19% lower than in healthy subjects matched for gender and age. In subjects with diabetes,  $t_{1/2}$  was approximately 3 hours shorter. These small pharmacokinetic differences should not warrant dose adjustment in this population (CSR LVAS).

#### Renal and Hepatic Insufficiency

Following single dose administration in subjects with mild or moderate renal impairment (creatinine clearance (CL<sub>cr</sub>) of 31 to 80 mL/min), plasma IC351 concentrations were higher than observed in healthy subjects. In subjects with moderate renal impairment, systemic exposure to Total IC710 was 3.5-fold higher than in healthy individuals and the

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Based on these studies, the sponsor designed and conducted six primary adequate and well-controlled studies on which the efficacy and safety of IC351 in the treatment of ED is primarily based. Three additional studies were conducted to examine the \_\_\_\_\_ IC351 so that appropriate dosing instructions could be determined. In addition to the open-label studies ( LVBD, LVBL, LVDR) in which efficacy and safety was evaluated, safety assessment of IC351 also included studies for sperm parameters and a US study (LVCD, LVCZ, LVCR) . In the open-label studies, patients received treatment with IC351 for up to 21 months.

Clinical pharmacology studies with IC351 were conducted in over 1000 patients. (42 completed studies). Studies for ED are categorized by sponsor ;as placebo-controlled (15 studies), studies with active control (3 studies), and uncontrolled (4 studies). As of march 2002 the sponsor has concluded studies LVCR, LVDR and LVCZ and provided the safety updates for these studies as well as the currently ongoing LVBL.

### 7. Clinical review methods

#### 7.1 How the review was conducted

This medical officer focused on the 6 pivotal studies for efficacy. For the review of safety and tolerability, 6 pivotal studies were reviewed closely while all other studies; open label, clinical pharmacology, market image at home formulations, were also reviewed. Special studies pertaining to cardiovascular, vision, sperm functions were also reviewed and appropriate consults were obtained from specific divisions. The statistical review of this was done by Dr. Hoberman. The accuracy of the sponsor's primary efficacy analyses for IIEF, SEP 2 and 3 were reviewed. Analyses and summary tables relating to major protocol violations, deaths, serious adverse events, and routine adverse events were reviewed using the data listings or electronic case report forms provided by the sponsor. The sponsor also provided safety updates that were reviewed.

#### 7.2. Overview of materials consulted in review

##### 7.2.1. Submissions to NDA 21-368

- *Original NDA 21-368 ; Submission date of june 23, 2001; Volumes 1.1 - 1.55 and the Electronic submission to the CDER, EDR*
- *Electronic case report forms (CRFs) and electronic case report tabulations (CRTs)*
- *Serial submission to NDA 21-368 (#003 and #004 - Safety updates)*
- *IND # 54553*

##### 7.2.2. Other materials reviewed

- *Annual Report for IND # \_\_\_\_\_ (Serial #018)*

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- Preliminary filing review for NDA 21-3 — — 3-month formulation
- All correspondence submitted to IND # ——— since submission of the annual report.
- All minutes of regulatory meetings and telephone conferences with sponsor that were located in hard-copy or electronic Division files for INDs #: — and
- Various related IND and NDA reviews.

### 7.3. Overview of methods used to evaluate data quality and integrity

#### 7.3.1 DSI audits of clinical sites

Two study centers that participated in the pivotal clinical trial **LVDJ** were audited by the Division of Scientific Investigation (DSI) in 2002. A DSI audit report was submitted on March 7, 2002 describing the inspection results from those two sites: ———

————— The inspections found a few minor irregularities, but the report concluded that data from these sites was acceptable for review.

#### Medical officer's comment:

The information provided to us in the DSI report of the inspection of these clinical sites supports the validity of the data submitted in NDA 21-368.

#### 7.3.2 Site monitoring

The sponsor :

- Provided instructional material to the study sites.
- Sponsored a start-up training session to instruct the investigators and study coordinators on the protocol, the completion of the clinical report forms, and study procedures.
- Made periodic visits to the study site.
- Were available for consultation and stayed in contact with the study site personnel by mail, telephone, and/or fax;
- Reviewed and evaluated clinical report form data and used standard computer edits to detect errors in data collection; and conducted quality review of database.

The sponsor periodically checked a sample of the patient data recorded against source documents at the study site. This study was audited by Lilly ICOS LLC Medical Quality Assurance (MQA) and/or regulatory agencies. Audit certificates were submitted. To ensure the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigators kept records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study.

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### 7.3.3 Central laboratories

#### 7.3.3.1

The following were used as central laboratories:

- A central laboratory, \_\_\_\_\_ performed all clinical laboratory assessments:
- A central reader at \_\_\_\_\_ read all electrocardiograms: \_\_\_\_\_

#### Medical officer's comment:

The overall quality control data submitted by were adequate to obtain a general impression of the quality of the laboratories.

### 7.4 Were trials conducted in accordance with accepted ethical standards?

Based on the IRB documents, the protocol design, the conduct and analysis of the trial and the reports of DSI audits and sponsor's internal auditing, it appears that this study was conducted within norms of current standards.

### 7.5 Evaluation of financial disclosure

Based on information submitted by the sponsor there were no financial conflict-of-interest issue

## 8. Integrated review of efficacy

IC351 was evaluated in six Randomized, Double-Blind, Placebo-Controlled Studies of Efficacy and Safety of IC351 Administered "On Demand" to Patients with Erectile Dysfunction. This included a well-controlled study performed in patients with diabetes. The well-controlled primary efficacy studies were conducted in the following countries: Argentina, Australia, Canada, Mexico, and Taiwan. Patients with African descent constituted only 0.9% of the population studied. These studies included the following doses against the placebo.

- 1 LVBK—10, 20 mg, conducted in Spain (Diabetic population)
- 2 LVBN—5, 10 mg, was conducted in Canada, Argentina, and Mexico.
- 3 LVCE—2.5, 5, 10 mg, was conducted in Canada.
- 4 LVCQ—20 mg, was conducted in Australia.
- 5 LVCO—10, 20 mg, was conducted in Taiwan.
- 6 LVDJ—10, 20 mg was conducted in Canada.

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### 8.1. Efficacy endpoints

According to the sponsors submission; the primary efficacy variables in individual studies were the IIEF Erectile Function domain, the percentage of "yes" responses to SEP Question 2, and the percentage of "yes" responses to SEP Question 3. Because for most studies there were multiple IC351 doses studied, there are multiple separate primary null hypotheses to compare each IC351 dose with placebo. Testing of these hypotheses was based on least-squares means for treatment-group contrasts within three models (one for each primary efficacy variable), where each model involves all treatment groups (placebo group and each IC351 dose group). The details of the models are described below. Within each study, to protect against Type I error, the p-values from treatment-group contrasts were adjusted by the method of Dunnett for the comparison of multiple doses with placebo.

- H01 : There is no difference in 20 mg IC351 versus placebo in change from baseline on the IIEF EF domain.
- H02 : There is no difference in 20 mg IC351 versus placebo in change from baseline on Question 2 of the SEP.
- H03 : There is no difference in 20 mg IC351 versus placebo in change from baseline on Question 3 of the SEP.

The null hypothesis concerning 20 mg IC351 versus placebo, namely  $H_0 = H_{01} \text{ or } H_{02} \text{ or } H_{03}$ , will be rejected if and only if  $H_{01}$ ,  $H_{02}$ , and  $H_{03}$  are all rejected. ANCOVA models were used to evaluate change-from-baseline efficacy variables, and the models included terms for baseline value of the efficacy variable, treatment group, pooled site, and the baseline-by-treatment-group interaction. P-values were based on least-squares means from Type III sums of squares, and for primary efficacy analyses, they were adjusted for multiplicity as described above. In any model, if the interaction was not significant (that is, if  $p > 0.10$ ), then it was removed from the model and the main effects model remained, from which the between-treatment-group p-value was obtained.

#### 8.1.1. Primary efficacy endpoints

The primary efficacy endpoints were:

- IIEF Erectile Function Domain
- SEP Question 2 (assessing the ability to penetrate the partner's vagina)
- SEP Question 3 (assessing the ability to maintain the erection).

The Erectile Function Domain defines the severity of ED as follows:

No ED (score 26-30), mild ED (score 22-25), mild to moderate ED (score 17-21), moderate ED (score 11-16), and severe ED (score 6-10). (Scores less than 6 indicate the patient did not have any sexual intercourse attempts during the assessment period.) The primary efficacy studies included patients with a clinical diagnosis of ED (that is, a diagnosis based on clinical criteria rather than IIEF criteria). Therefore, patients of all severities were included and were not excluded based on their baseline

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IIEF Erectile Function Domain score. The aggregated version groups the no ED, mild ED, and mild to moderate ED into a single category of mild ED (score 17-30) and combines patients with scores less than 6 with the severe category (score 1-10).

### 8.1.2. Secondary (supportive) efficacy endpoints

1. IIEF Questions 3 and 4 were secondary variables in the primary IC351 efficacy studies.

These questions assess the patient's ability to penetrate his partner and maintain his erection following penetration. Question 3 asked, "Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?"

Question 4 asked, "Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you penetrated (entered) your partner?"

#### 2. IIEF Intercourse Satisfaction and Overall Satisfaction Domains

The IIEF Intercourse Satisfaction and Overall Satisfaction Domains were secondary variables in all IC351 primary efficacy studies. The Intercourse Satisfaction Domain queries the patient on frequency, satisfaction, and enjoyment of intercourse during the assessment period. The Overall Satisfaction Domain queries the patient on his satisfaction with his overall sex life and his sexual relationship with his partner.

3. SEP Questions 4 and 5 were secondary variables and asked if the patient was satisfied with the hardness of his erection and with his overall sexual experience, respectively.

#### 4. Partner SEP

The partner SEP had three questions. Question 1 asked whether the patient could achieve at least some erection. Questions 2 and 3 were secondary variables in the LVBN, LVCE, and LVDJ studies. These questions asked whether the patient could insert his penis into his partner's vagina and whether the partner was satisfied with the overall sexual experience.

#### 5. Global Assessment Questions (GAQ)

The GAQ was a secondary variable in all primary IC351 efficacy studies. The GAQ was self-administered at the end of the treatment period (or early termination). Two questions were asked. First, the patient was asked if the treatment taken during the study improved his erections. If the patient answered yes to the first question, the patient was then asked if the treatment improved his ability to engage in sexual activity.

### 8.2. Populations analyzed

Analyses were performed for the intent-to-treat (ITT) data-sets. These populations were defined as follows:

#### 8.2.1. ITT population

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**Primary and secondary analyses** were done on an intent-to-treat basis. An intent-to-treat analysis is an analysis of data by the groups to which patients are assigned by random allocation, even if the patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. The analysis population for efficacy analyses of any particular efficacy variable was all patients with both baseline and post baseline data for that efficacy variable.

Last-observation-carried-forward (LOCF) models were used to evaluate efficacy data. The primary efficacy analyses were performed on the original scale data (using change from baseline) unless the assumptions of the model appeared to be violated, in which case rank-transformed data were considered for analysis.

Investigative sites with low enrollment were pooled by geographical proximity by an algorithm determined a priori. All efficacy analyses were performed using the identical pooled sites.

### 8.2.2. "Observed-cases" population

This data -set was not collected or analysed.

### 8.3 Handling of dropouts or missing data

Missing data were handled as follows for the intent-to-treat population: Patients with baseline data only (i.e., no on-study efficacy data) were not included in the analysis.

The analysis population for efficacy analyses of any particular efficacy variable was all patients with both baseline and post baseline data for that efficacy variable.

Last-observation-carried-forward (LOCF) models were used to evaluate efficacy data.

The primary efficacy analyses were performed on the original scale data (using change from baseline) unless the assumptions of the model appeared to be violated, in which case rank-transformed data were considered for analysis.

### Medical Officers Comments:

The Efficacy variables, population and methods of analyses are acceptable.

### 8.4. Principal clinical trials to support efficacy claim:

IC351 was evaluated in six Randomized, Double-Blind, Placebo-Controlled Studies of Efficacy and Safety of IC351 Administered \_\_\_\_\_ to Patients with Erectile Dysfunction. This included a well-controlled study performed in patients with diabetes. These studies were individually reviewed. Please note that the Objectives, general demographics, Entry criteria, primary and secondary endpoints, design, and conduct were similar across the studies. The sponsor selected all spectrum of ED patients and demographic characteristics were homogenized to mimic the ED population in US. For the sake of repetitiveness common features are not described for every study. The sponsors submitted 2 other studies, LVCK and LVDG looking at \_\_\_\_\_ and \_\_\_\_\_. These were also reviewed.

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### 8.4.1. Clinical Trial H6D-MC-LVCE (P-2.5mg-5mg-10mg)

**("A Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of IC351 (LY450190) Administered "On Demand" to Patients with Erectile Dysfunction") (Trial start March 17, 2000; Trial completion August 18, 2000)**

**Objectives:** Primary objectives: 1) to evaluate the efficacy of IC351 at doses of 2.5 mg, 5 mg, and 10 mg, in comparison with placebo, when taken "on demand" over 12 weeks in improving erectile function as measured by the Erectile Function Domain of the IIEF (Questions 1-5 and 15), Question 2 of the Sexual Encounter Profile (SEP) diary, and Question 3 of the SEP diary and 2) to determine the safety of IC351 in men with ED.

Secondary objectives: 1) to evaluate the efficacy of IC351 in comparison with placebo in men with ED using other variables including responses to the Global Assessment Questions, the SEP for patient and partner, and the IIEF, including Questions 3 and 4 2) to characterize the population pharmacokinetics of IC351 and to identify covariates that may significantly influence the disposition of IC351 in men with ED and 3) to characterize the population pharmacodynamics of IC351 and to identify covariates that may significantly influence the response variables (IIEF Erectile Function domain, IIEF Question 3, IIEF Question 4, patient SEP Question 2, and patient SEP Question 3 in men with ED.

**Design and conduct summary:** The study was a multicenter (18 sites in Canada), randomized, double-blind, placebo-controlled, parallel design trial to evaluate the safety and efficacy of intermittent "on demand" dosing of three different doses of IC351 or placebo administered for 12 weeks to men with ED. The study population consisted of men at least 21 years of age who reported at least a 3 month history of erectile dysfunction with a range of severity (mild to severe) and etiological classification (psychogenic, organic, and mixed psychogenic and organic). Three hundred eight patients were randomized (79 to placebo, 74 to 2.5 mg IC351, 79 to 5.0 mg IC351, and 79 to 10 mg IC351).

The study consisted of 2 phases. The first phase was a screening and run-in phase which lasted approximately 4 weeks. At Visit 1 the patient and his partner signed an informed consent. After the 4 week run-in period, patients returned for visit 2 if they fulfilled inclusion and exclusion criteria. The patients were then randomized to placebo or 2.5, 5.0, or 10 mg of study drug. They then entered a treatment phase which lasted 12 weeks. Patients were evaluated at each month of the 12 week treatment period (Visits 3, 4, and 5). The IIEF and SEP were administered at Visit 2 (baseline), Visits 3 and 4 (interim analysis), and Visit 5 (end of treatment). Vital signs and clinical laboratory analyses were performed at each visit. ECG's were performed at visits 1 and 5. To determine plasma IC351 concentrations for pharmacokinetic analyses, two blood samples were drawn from all patients at Visit 3, Visit 4, and Visit 5. For these determinations, the patient was asked to take a single dose of drug at specific times prior to the visit.

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**Study population:** The study population was men at least 21 years of age who reported at least a 3 month history of erectile dysfunction. Study population baseline characteristics are shown in Table 5.

**Table 5: LVCE . Baseline characteristics of randomized patients.**

	Placebo (n=76)	IC351 2.5 mg (n=74)	IC351 5.0 mg (n=79)	IC351 10 mg (n=79)
Age (mean)	56.9	60.4	57.7	56.8
IIEF ED domain (mean)	13.3	13.3	12.4	14.6

Over 90% of patients in all groups were Caucasian.

**Inclusion and exclusion criteria:**

Inclusion criteria included:

1) men at least 21 years of age 2) history of ED for at least 3 months prior to visit 1 3) made at least 4 sexual intercourse attempts during the 4 week run-in period without medication.

Exclusion criteria included:

1) ED caused by untreated endocrine disease 2) history of radical prostatectomy (with the exception of bilateral nerve-sparing prostatectomy) 3) history of penile implantation 4) evidence of clinically significant renal insufficiency 5) evidence of clinically significant hepato-biliary disease (SGOT or SGPT > 3 x ULN) 6) hemoglobin A1c >13% 7) patients with chronic stable angina treated with long acting nitrates or patients with chronic stable angina who have required short-acting nitrates in the prior 90 days 8) unstable angina within prior 6 months, history of myocardial infarction or coronary artery bypass graft surgery within 90 days or percutaneous coronary intervention within 90 days 9) supraventricular arrhythmia with an uncontrolled ventricular response (HR > 100 bpm) at rest despite medical therapy, history of sustained ventricular tachycardia (HR > 100 bpm for > 30 seconds) despite medical therapy, presence of internal cardioverter-defibrillator 10) congestive heart failure within 6 months 11) new, significant cardiac conduction abnormality within 90 days 11) systolic blood pressure >170 or < 90 mmHg or diastolic blood pressure > 100 or < 50 mmHg 12) significant central nervous system disease within past 6 months 13) current treatment with nitrates, cancer chemotherapy, or anti-androgens.

**Primary and secondary endpoints:** Primary endpoints: 1) IIEF Erectile Function domain, which consists of the sum of questions 1-5 and 15 of the IIEF 2) percentage of "yes" responses to Question 2 of the SEP ("Were you able to insert your penis into your partner's vagina?") and 3) percentage of "yes" responses to Question 3 of the SEP ("Did your erection last long enough for you to have successful intercourse?") Secondary endpoints: 1) Questions 3 and 4 of the IIEF 2) percentage of "yes" responses to

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questions 4 and 5 of the SEP and to Questions 1, 2, and 3 of the partner SEP diary and 3) Global Assessment Questions.

**Withdrawals, compliance, and protocol violations:** The majority (89.9%) of patients completed the trial. Four patients discontinued because of an adverse event (3 in the 2.5 mg drug group and 1 in the 10 mg drug group).

**Efficacy analysis:**

The results of the primary efficacy analyses are shown in Table 6:

**Table 6-LVCE : Summary of primary efficacy analyses**

	Placebo End (change)	IC351 (2.5 mg) End (change)	IC351 (5.0 mg) End (change)	IC351 (10 mg) End (change)
ED domain of IIEF	14.4 (+1.1)	16.6 (+3.2) p=.154	17.5 (+5.1) p=.002	20.6 (+6.0) p<.001
SEP 2	45.9 (+2.4)	55.9 (+15.3) p=0.31	55.9 (+17.6) p=0.008	68.4 (+15.1) p=.001
SEP 3	27.8 (+3.5)	37.2 (+19.7) p=.014	41.5 (+24.0) p<.001	51.1 (+25.8) p<.001

***Medical Officer's comments:***

The 5.0 and 10 mg doses (but not the 2.5 mg dose) were statistically superior to placebo in all of the three primary endpoints. All three doses used in this trial are lower than the proposed dose of 20 mg.

**Safety analysis:**

**Extent of exposure:** The mean doses of drug taken per week were 2.0, 2.1, 2.1, and 2.1 for the placebo, 2.5 mg, 5.0 mg, and 10 mg groups, respectively.

**Serious adverse events:**

No deaths occurred during the study.

Four patients experienced serious adverse events; none of these events was thought to be related to study drug by the investigator. Two patients with lung cancer were discontinued from the study. One patient had a deep venous thrombosis and one had pancreatitis and both continued the study.

***Medical Officer's comments:*** *The reviewer agrees that none of these SAE's was likely related to study drug.*

**Discontinuations due to adverse event:** Four patients discontinued the study because of an adverse event. Two had lung cancer, one had shoulder pain, and one a "pinched-nerve."

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**Frequent adverse events:** There were no statistically significant differences between the 4 groups in the incidence of any specific adverse event. Headache and dyspepsia showed a dose related increase in incidence. Table 7.

**Table 7: LVCE Most Frequent Adverse Events**

	Placebo (n=76)	IC351 2.5 mg (n=74)	IC351 5.0 mg (n=79)	IC351 10 mg (n=79)
Headache	6 (7.9%)	5 (6.8%)	13 (6.5%)	11 (13.9%)
Infection	5 (6.6%)	4 (5.4%)	4 (5.1%)	7 (8.9)
Dyspepsia	3 (3.9%)	1 (1.4%)	5 (6.3%)	8 (10.1%)
Pain	4 (5.3%)	4 (5.4%)	5 (6.3%)	3 (3.8%)
Back pain	4 (5.3%)	3 (4.1%)	3 (3.8%)	3 (3.8%)
Dizziness	1 (1.3%)	2 (2.7%)	2 (2.5%)	3 (3.8%)

One patient in the 10 mg IC351 group experienced a rash on his forehead which was interpreted by the investigator as an allergic reaction to study drug. Among the 10 patients who experienced a non-serious clinically significant adverse event but continued the study were one patient with "eye disorder" and one patient with "eye pain." The patient with "eye disorder" experienced "mild eye itching" after taking the first two drug doses. The patient with "eye pain" experienced "eye pressure, nasal congestion, and sinus pain" on 3 occasions after each dose of drug he took. He discontinued from the study because of lack of efficacy.

No adverse events related to color vision disturbances were reported.

### **Changes in laboratory values:**

Criteria for clinically significant laboratory values were not established in this study.

Clinically significant laboratory values were determined by each investigator. No clinically significant change in laboratory values was reported for any patient.

### **MISCELLANEOUS:**

In the subgroup < age 65, there were no statistically significant differences among treatment groups in the mean change from baseline to endpoint in any vital sign. For the subgroup of patients > age 65, the 10 mg drug group showed mean changes in sitting systolic and diastolic blood pressure of -8.7 and -8.6 mmHg, respectively. The sponsor does not consider these changes relevant because of a lack of standardized blood pressure measurements in this trial, absence of a relationship to dose or dosing, small sample size in the subgroups, and the higher baseline values in the 10 mg IC351 group.

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### **Medical Officer's assessment of efficacy and safety:**

The doses of IC351 used in this trial are less than the proposed 20 mg dose. The 5 and 10 mg doses show efficacy. No major safety concerns are raised, but the maximum dose in this trial is 10 mg.

### **8.4.2. Clinical Trial H6D-MC-LVBN (P- 5mg-10 mg)**

**Title: A Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of IC351 (LY450190) Administered "On Demand" to Patients with Male Erectile Dysfunction. (Dates of Study: 10 December 1999 through 31 May 2000.)**

#### **Objectives:**

##### Primary objectives:

1) to evaluate the efficacy of IC351 at doses of 5 mg and 10 mg, in comparison with placebo, when taken "on demand" over 12 weeks in improving erectile function as measured by the Erectile Function Domain of the IIEF (Questions 1-5 and 15), Question 2 of the Sexual Encounter Profile (SEP) diary, and Question 3 of the SEP diary and 2) to determine the safety of IC351 in men in argentina, canada and mexico. with ED.

##### Secondary objectives:

To evaluate the efficacy of IC351 in comparison with placebo in men with erectile dysfunction using other variables including responses to the Global Assessment Questions (GAQ), the SEP for patient and partner, and the IIEF.

#### **Design and conduct summary:**

The study was a multicenter (Study Centers: There were 17 centers involved in this study. Investigators: 19), randomized, double-blind, placebo-controlled, parallel design trial to evaluate the safety and efficacy of intermittent "on demand" dosing of two different doses of IC351 or placebo administered for 12 weeks to men with ED. The study population consisted of men at least 18 years of age who had a monogamous relationship with a female sexual partner and a history of erectile dysfunction at least 3 months in duration ranging in severity (mild to severe) and etiological classification (psychogenic, mixed, organic) : Male 146 Placebo: Male 69.

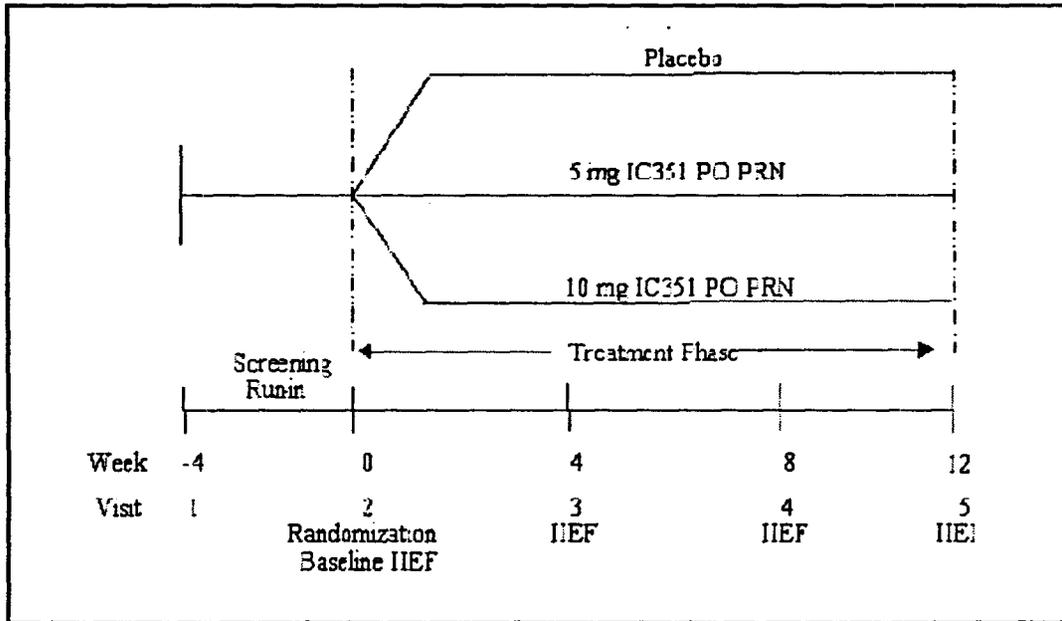
The study consisted of 2 phases. The first phase was a screening and run-in phase which lasted approximately 4 weeks. At visit 1 the patient and his partner signed an informed consent. After the 4 week run-in period, patients returned for visit 2 if they fulfilled inclusion and exclusion criteria. The patients were then randomized to placebo or 5 or 10 mg of study drug. They then entered a treatment phase which lasted 12

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weeks. Patients were evaluated at each month of the 12 week treatment period (Visits 3, 4, and 5). The IIEF and SEP were administered at Visit 2 (baseline), Visits 3 and 4 (interim analysis), and Visit 5 (end of treatment). Vital signs and clinical laboratory analyses were performed at each visit. (Study design is presented in fig 2)

Figure 2 :STUDY DESIGN :LVBN



**Demographics:** The mean age was 57 years in the placebo group, 60 years in the 5-mg IC351 group, and 59 years in the 10-mg IC351 group. The number of patients who were Caucasian was 56 (81%) in the placebo group, 60 (83%) in the 5-mg IC351 group, and 61 (82%) in the 10-mg IC351 group. The most common etiology of ED was organic, accounting for 44 patients (64%) in the placebo group, 47 patients (65%) in the 5-mg IC351 group, and 49 patients (66%) in the 10-mg IC351 group. The mean IIEF Erectile Function domain score at baseline was 14.5 in the placebo group, 13.8 in the 5-mg IC351 group, and 14.3 in the 10-mg IC351 group. 19 centers in Argentina, Canada and Mexico participated in this study.

**Study population:** This study was conducted in 3 countries. (Table 8)

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**Table 8 :LVBN: Summary of Patient Enrollment (Source LVBN10.1)**

Patients Entered	Patients Enrolled (Randomized)				
	Country/site	Placebo	IC_5mg	IC_10mg	Total
	n (%)	n (%)	n (%)	n (%)	
<b>Argentina</b>					
95	26 (37.7)	27 (37.5)	28 (37.8)	81 (37.7)	
35	10 (14.5)	11 (15.3)	11 (14.9)	32 (14.9)	
8	2 (2.9)	2 (2.8)	3 (4.1)	7 (3.3)	
14	5 (7.2)	4 (5.6)	4 (5.4)	13 (6.0)	
4	0 (0)	0 (0)	0 (0)	0 (0)	
32	9 (13.0)	10 (13.9)	10 (13.5)	29 (13.5)	
2	0 (0)	0 (0)	0 (0)	0 (0)	
<b>CANADA(#)</b>					
113	33 (47.8)	36 (50.0)	35 (47.3)	104 (48.4)	
10	3 (4.3)	3 (4.2)	4 (5.4)	10 (4.7)	
11	3 (4.3)	3 (4.2)	4 (5.4)	10 (4.7)	
10	3 (4.3)	3 (4.2)	3 (4.1)	9 (4.2)	
16	5 (7.2)	5 (6.9)	5 (6.8)	15 (7.0)	
10	3 (4.3)	4 (5.6)	2 (2.7)	9 (4.2)	
8	2 (2.9)	3 (4.2)	2 (2.7)	7 (3.3)	
14	4 (5.8)	4 (5.6)	4 (5.4)	12 (5.6)	
14	4 (5.8)	4 (5.6)	5 (6.8)	13 (6.0)	
10	3 (4.3)	3 (4.2)	3 (4.1)	9 (4.2)	
10	3 (4.3)	4 (5.6)	3 (4.1)	10 (4.7)	
<b>MEXICO(#)</b>					
33	10 (14.5)	9 (12.5)	11 (14.9)	30 (14.0)	
16	5 (7.2)	4 (5.6)	5 (6.8)	14 (6.5)	
4	1 (1.4)	1 (1.4)	1 (1.4)	3 (1.4)	
13	4 (5.8)	4 (5.6)	5 (6.8)	13 (6.0)	
<b>241</b>	<b>69</b>	<b>72</b>	<b>74</b>	<b>215</b>	

**Patient Selection Criteria:**

Inclusion criteria included: 1) men at least 21 years of age 2) history of ED for at least 3 months prior to visit 1 3) made at least 4 sexual intercourse attempts during the 4 week run-in period without medication.

Exclusion criteria included: 1) ED caused by untreated endocrine disease 2) history of radical prostatectomy (with the exception of bilateral nerve-sparing prostatectomy) 3) history of penile implantation 4) evidence of clinically significant renal insufficiency 5) evidence of clinically significant hepato-biliary disease (SGOT or SGPT > 3 x ULN) 6) hemoglobin A1c >13% 7) patients with chronic stable angina treated with long acting

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nitrites or patients with chronic stable angina who have required short-acting nitrites in the prior 90 days 8) unstable angina within prior 6 months, history of myocardial infarction or coronary artery bypass graft surgery within 90 days or percutaneous coronary intervention within 90 days 9) supraventricular arrhythmia with an uncontrolled ventricular response (HR > 100 bpm) at rest despite medical therapy, history of sustained ventricular tachycardia (HR > 100 bpm for > 30 seconds) despite medical therapy, presence of internal cardioverter-defibrillator 10) congestive heart failure within 6 months 11) new, significant cardiac conduction abnormality within 90 days 11) systolic blood pressure > 170 or < 90 mmHg or diastolic blood pressure > 100 or < 50 mmHg 12) significant central nervous system disease within past 6 months 13) current treatment with nitrites, cancer chemotherapy, or anti-androgens.

### **Primary and secondary endpoints:**

Primary endpoints: 1) IIEF Erectile Function domain, which consists of the sum of questions 1-5 and 15 of the IIEF 2) percentage of "yes" responses to Question 2 of the SEP ("Were you able to insert your penis into your partner's vagina?") and 3) percentage of "yes" responses to Question 3 of the SEP ("Did your erection last long enough for you to have successful intercourse?") Secondary endpoints: 1) Questions 3 and 4 of the IIEF 2) percentage of "yes" responses to questions 4 and 5 of the SEP and to Questions 1, 2, and 3 of the partner SEP diary and 3) Global Assessment Questions.

**Withdrawals, compliance, and protocol violations:** The majority (89.9%) of patients completed the trial. Four patients discontinued because of an adverse event (3 in the 2.5 mg drug group and 1 in the 10 mg drug group).

**Efficacy analysis:** This study showed a change of 5.6, 29 and 31.7 from the base line in 10mg dose patients in IIEF, SEP2 and SEP3 respectively .Table 9

**Table 9: Efficacy analysis: LVBN**

Efficacy Analysis LVBN (Source Table ISE 2.5)

EFF. Variable	All Patients n=215	Placebo N=69	IC =5mg N=72	IC 10mg N=74
	Base line	CHG	CHG	CHG
IIEF	14.2	0.7	4**	5.6*
SEP 2	43.3	5.6	14.5***	29*
SEP3	22.6	3.7	19.0****	31.7*

\*p< .001, \*\*p< .006. \*\*\*p< .064, \*\*\*\*p< .040

### **Medical officers Comments:**

10 mg dose showed statistically significant efficacy in all 3 primary end points.  
5 mg dose showed statistically significant efficacy in IIEF and SEP3 scores, but did not

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reach statistical significance in SEP 2 ( $p < .064$ )

### Study discontinuation:

Table 10 summarizes the study discountinuations

**Table 10: LVBN Study discontinuation(source Table LVBN. 10. 2.)**

Status	Placebo (N=69)		IC 5mg (N=72)		IC 10mg (N=74)		Total (N=215)	
	n	(%)	n	(%)	n	(%)	n	(%)
Protocol completed	58	(84.1)	66	(91.7)	65	(87.8)	189	(87.9)
Adverse event	2	(2.9)	1	(1.4)	2	(2.7)	5	(2.3)
Lack of efficacy, patient perception	0		2	(2.8)	0		2	(0.9)
Unable to contact patient (lost to follow-up)	6	(8.7)	1	(1.4)	2	(2.7)	9	(4.2)
Personal conflict or other patient decision	1	(1.4)	1	(1.4)	3	(4.1)	5	(2.3)
Protocol entry criteria not met	0		0		1	(1.4)	1	(0.5)
Physician decision	1	(1.4)	0		0		1	(0.5)
Protocol Violation	1	(1.4)	1	(1.4)	1	(1.4)	3	(1.4)

### Protocol violations:

Common protocol violations included patient and partner diaries being completed incorrectly (Sites 201, 202, 204, 205, 206, 208, 209, 211, 212, 213, 218, 220, and 222), patients not taking the study medication appropriately (Sites 201, 202, 203, 206, 208, 211, 212, and 220), patients who did not have physical exams according to the protocol (Sites 203, 205, 207, and 213), patients who had visit window violations (Sites 202, 203, 204, 206, 207, 208, 211, 213, 216, 218, 219, and 220), patients who did not complete the IIEF as required by the protocol (Sites 208, 209, and 211), informed consent not being administered according to the protocol (Sites 201, 202, 208, 211, 212, 213, and 220), and various other protocol procedures not performed according to the protocol (Sites 205, 211, 212, and 220). Other protocol violations included 2 patients who did not have Visit 1 urine samples analyzed (Site 202), 2 patients who did not complete the Visit 2 IIEF (Sites 203 and 204), several patients with missing labs (Site 205, 207, and 218), patients who did not return study medication materials (Site 207, 209, and 218) and 1 patient who did not have an ECG at Visit 5 (Site 220).

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There were several violations of inclusion or exclusion criteria. Two patients who had not had four sexual attempts recorded in their patient diaries at Visit 2 were randomized at Site 218. Patients who did not have their HbA1c analyzed were randomized at Sites 204 and 218. There were patients at Sites 208 and 222 who developed exclusionary blood pressure values and were not discontinued immediately. Finally, Site 203 did not discontinue a patient when his blood pressure became exclusionary at Visit 4.

### **Medical officers Comments:**

Protocol violations described here did not significantly impact on patient safety, data integrity, or conclusions drawn from the study.

### **Safety Evaluation:**

#### **Extent of Exposure:**

The evaluation of safety includes all 215 enrolled patients on an intent-to-treat basis. This was an "on demand" study in which patients were given study drug to take on an as-needed basis for a period of 12 weeks. Patients were to take one dose prior to expected sexual activity, and not to exceed more than one dose daily. Patients were randomized to treatment as follows: 69 to placebo, 72 to 5 mg IC351, and 74 to 10 mg IC351. The mean doses taken per week were 1.8 for placebo, 1.8 for 5-mg IC351, and 2.0 for 10-mg IC351.

#### **Adverse Events**

The most common treatment-emergent adverse events in the IC351 patients were headache, back pain, rhinitis, and dyspepsia.

#### **Treatment-Emergent Adverse Events**

The most common treatment-emergent adverse events in the IC351 patients were headache, back pain, rhinitis, and dyspepsia. Headache occurred in 8 patients (10.8%) in the 10 mg IC351 group and 3 patients (4.3%) in the placebo group. Back pain occurred in 5 patients (6.8%) in the 10 mg IC351 group and 2 patients (2.9%) in the placebo group. Rhinitis occurred in 5 patients (6.8%) in the 10 mg IC351 group and 0 patients (0.0%) in the placebo group. Dyspepsia occurred in 4 patients (5.4%) in the 10 mg IC351 group and 2 patients (2.9%) in the placebo group. The incidence of treatment-emergent adverse events was higher in the 10-mg IC351 group (51.4%) than in each of the 5-mg IC351 (36.1%) and placebo (40.6%) groups; however, there was no statistically significant difference in treatment groups in the overall incidence of treatment-emergent adverse events.

#### **Vital Signs Laboratory Parameters**

Statistically significant differences among treatment groups were observed in the mean

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change from baseline to endpoint in urea nitrogen, cholesterol, and bilirubin; from baseline to minimum in cholesterol and hematocrit; and from baseline to maximum in AST/SGOT and monocytes. None of these changes were clinically significant. No clinically significant changes occurred in vital signs.

### Clinically Significant Abnormalities

Patient 6626 at Site 216 discontinued due to abnormally high levels of hepatic enzymes, which were attributed to cholelithiasis and unrelated to study drug.

### **Medical Officers comment:**

The reviewer agrees with the sponsors assessment.

### Deaths

No deaths occurred in the present study.

### Serious Adverse Events

One patient experienced a serious adverse event. The patient received placebo and developed acute abdominal syndrome (acute appendicitis). For this patient, abdominal pain, acute abdominal syndrome, and peritonitis were listed as permanently disabling ; however, these were coding errors, as the patient recovered.

### Non Serious Clinically Significant Adverse Events

Five patients experienced a non serious clinically significant adverse event during this study. A total of 4 patients (1 placebo, 3 IC351) discontinued due to non serious adverse events. The discontinuation from the placebo group was a case of emotional reaction due to lack of efficacy. The discontinuations in the IC351 patients included a case of paraesthesia, a case of back pain, and a case of dyspepsia . One additional patient who received IC351 experienced clinically significant adverse events (two episodes of palpitations) and remained on the study.

### Summary of Patient events:

Patient 2109 at Site 201 had two episodes of palpitations during the course of this study. For one year this patient has had mild erectile dysfunction that is organic in etiology. Approximately 1 hour after taking the first two doses of study medication (10 mg IC351, 12-Jan-00 and 13-Jan-00) this patient experienced facial flushing, dizziness, and palpitations. These episodes lasted approximately 2 hours. With the patient's third dose of medication (31-Jan-00) the patient reported only facial flushing. Throughout the remainder of the study the patient took 13 doses without incident. This patient has a history of high blood pressure, which was recorded as 160/80 at Visits 1 through 3. This patient's blood pressure was poorly controlled at the time of the episodes of palpitations, and the patient was scheduled to be assessed by his family doctor to determine if his blood pressure could be brought under control. The patient was allowed

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to continue in the trial.

Patient 2307 at Site 203 discontinued his participation from the study as a result of middle back pain of moderate intensity. This patient has had erectile dysfunction for one year that is moderately severe and with an organic etiology. One to two hours after taking 10 mg IC351 (3 doses taken), this patient experienced moderate middle back pain and mild abdominal pain, for which he did not seek symptomatic relief. The back pain was described as muscular cramps that started in the middle of the patient's back and traveled down his legs. The patient reported problems with sleeping and inability to stretch his legs during the episodes. The pain lasted for 2 days. Upon his return to the investigator's site for his scheduled visit, he indicated to staff that he did not want to participate in the study any longer due to the back ache. He was thus discontinued.

Patient 2507 at Site 205 discontinued his participation from the study as a result of paresthesia of the right trunk, neck and face. This patient has had erectile dysfunction for one year that is moderately severe and with an organic etiology. The patient took a total of 3 doses of study medication (5 mg IC351) on the following dates 15-Jan-00, 22-Jan-00 and 29-Jan-00. Sexual attempts were only made after the last two doses. The patient developed paresthesia of the right trunk, neck and face on 30-Jan-00 that was still present when the patient returned to the investigator's site for an early discontinuation visit on 04-Feb-00. The patient also experienced a dizziness episode on 03-Feb-00. The patient was discontinued from the study at the patient's request on 04-Feb-00. The patient saw his family doctor after discontinuing the trial and arrangements had been made for a neurological assessment and consult (had CT booked for 12-Jun-00). This assessment did not occur since the patient was hospitalized on — as a result of a myocardial infarct. At screening, the patient had the following high lab values: ALT 52 U/L (6-34 U/L); GGT 185 U/L (10-61U/L). At the randomization visit the same lab values were still high (ALT 64 U/L, GGT 223 U/L), AND THE NF-GLU was high at 18.5 MMOL/L (2.8-13.9 MMOL/L). AT VISIT 3 the following lab values were still high: ALT 53 U/L; GGT 220 U/L; NF-Glu 14.3 mmol/L. At the discontinuation visit the patient had the following high lab values: ALT 49 U/L; GGT 210 U/L; NF-Glu 15.7 mmol/L. At screening and discontinuation visits the patient was positive for urinary glucose.

Patient 2408 at Site 204 discontinued his participation from the study as a result of dyspepsia. This patient has had erectile dysfunction for one year that is severe and with an organic etiology. This patient had taken a total of 6 doses of 10 mg IC351. With the last two doses of study medication (16-Feb-00 and 21-Feb-00) he experienced severe heartburn that lasted into the following day. The patient confirmed that he had not increased his consumption of alcohol, coffee, chocolate or oily foods from his normal intake during this period of time. The severe heartburn was also accompanied by mild left arm pain that the patient did not believe to be cardiovascular in nature. Upon his return to the investigator's site for his scheduled visit, he indicated to staff that he did not want to participate in the study any longer due to the dyspepsia. He was thus discontinued.

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Patient 6626 at Site 216, randomized to receive IC351 10 mg, had mildly elevated ALT at Visits 1 and 2 of 92 U/L and 97 U/L, respectively (less than 3 times the upper limit of normal). After approximately 8 weeks of therapy during which time he took 11 doses of study drug, his ALT rose to 141 U/L (greater than 3 times the upper limit of normal), associated with an increase in AST of 56 U/L and GGT of 95 U/L. The patient was discontinued from the study because of the elevated hepatic enzyme levels, which were assessed by the investigator as not related to study drug. Subsequently, the patient was diagnosed with cholelithiasis and was scheduled for surgery.

### **Medical Officers Overall assesment of safety and efficacy :**

Both 5 and 10 mg significantly improved ED.

There were no deaths reported

There was no SAE directly attributable to the drug.

Both 5 mg and 10 mg doses appeared to be well tolerated , however the sponsor seeks 20mg dose.

### **8.4.3. Clinical Trial H6D-MC-LVBK (PI-10mg-20mg)**

**“A Randomized, Double-Blind, Placebo-Controlled Study of IC351 (LY450190) Administered “On Demand” to Male Diabetics with Erectile Dysfunction”) (Trial start December 28, 1999; Trial completion August 17, 2000)**

**Objectives:** Primary objectives: 1) to evaluate the efficacy of IC351 in comparison to placebo in improving erectile function in diabetic men as measured by the Erectile Function domain of the International Index of Erectile Function (IIEF, Questions 1-5 and 15), Question 2 of the Sexual Encounter Profile (SEP) diary, and Question 3 of the SEP diary and 2) to determine the safety of IC351 in diabetic men with erectile dysfunction. Secondary objectives: to evaluate the efficacy of IC351 in comparison with placebo in diabetic men with erectile dysfunction using other variables including responses to the Global Assessment Questions, the SEP diary, and the IIEF.

**Design and conduct summary:** The study was a multicenter (18 sites in Spain), randomized, double-blind, placebo-controlled, parallel design trial to evaluate the safety and efficacy of intermittent “on demand” dosing of two different doses of IC351 (10 and 20 mg) or placebo administered for 12 weeks to male diabetics with ED. The study population consisted of men at least 18 years of age with Type 1 or Type 2 diabetes mellitus who reported at least a 3 month history of erectile dysfunction. Two hundred sixteen patients were randomized (10 mg IC351 : 73 patients; 20 mg IC351 : 72 patients; and placebo : 71 patients).

The study consisted of 2 phases. The first phase was a screening and run-in phase which lasted approximately 4 weeks. At visit 1 the patient and his partner signed an

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informed consent. After the 4 week run-in period, patients returned for visit 2 if they fulfilled inclusion and exclusion criteria. The patients were then randomized to placebo or 10 or 20 mg of study drug. They then entered a treatment phase which lasted 12 weeks. Patients were evaluated at each month of the 12 week treatment period (Visits 3, 4, and 5). The IIEF and SEP were administered at Visit 2 (baseline), Visits 3 and 4 (interim analysis), and Visit 5 (end of treatment). Vital signs and clinical laboratory analyses were performed at each visit. ECG's were performed at visits 1 and 5.

**Study population:** The study population was men with Type 1 or Type 2 diabetes mellitus at least 18 years of age who reported at least a 3 month history of erectile dysfunction. Study population baseline characteristics are shown in Table 11.

**Table 11: LVBK Baseline characteristics of randomized patients**

	Placebo (n=71)	IC351 10 mg (n=72)	IC351 20 mg (n=73)
Age (years) (mean)	55.8	55.9	55.5
Ethnicity (%)			
Caucasian	98.6	100	100
IIEF ED domain	12.1	12.9	11.5
Diabetes type (%)			
Type 1	11.3	11.0	5.6
Type 2	88.7	89.0	94.4
Hb A1c	8.23	8.21	8.30

**Medical Officer's comment:** The baseline characteristics of the three study groups are comparable.

**Inclusion and exclusion criteria:**

Inclusion criteria included: 1) men at least 18 years of age 2) history of ED (defined as a consistent change in the quality of erection that adversely affects the patient's satisfaction with sexual intercourse) for at least 3 months prior to visit 1 3) made at least 4 sexual intercourse attempts during the 4 week run-in period without medication 4) clinical diagnosis of Type 1 or Type 2 diabetes mellitus 5) hemoglobin A1C < 13.0% at Visit 1 .

Exclusion criteria included: 1) ED caused by untreated endocrine disease 2) history of radical prostatectomy 3) history of penile implantation 4) uncontrolled diabetes mellitus defined as two or more episodes of ketoacidosis within 1 year prior to Visit 1 or one episode of ketoacidosis within 3 months prior to Visit 1 5) uncontrolled diabetes mellitus defined as 3 or more episodes of hypoglycemia requiring assistance as defined by the Diabetes Control and Complications Trial 6) significantly impaired renal function as

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defined by a serum creatinine value greater than 2.5 mg/dL, or who have received a renal transplant, or are currently being treated with either hemodialysis or peritoneal dialysis 7) anemia defined as a hemoglobin <10.5 g/dL 8) evidence of clinically significant hepato-biliary disease as evidenced by SGOT or SGPT > 3 x ULN at Visit 1 9) patients with chronic stable angina treated with long acting nitrates or patients with chronic stable angina who have required short-acting nitrates in the prior 90 days or angina occurring during sexual intercourse within the last 6 months 8) unstable angina within prior 6 months, history of myocardial infarction or coronary artery intervention within the past 6 months 9) any cardiac arrhythmia treated medically or with a device including implanted defibrillators, significant conduction defects, pacemakers, or any history of congestive heart failure 10) systolic blood pressure >170 or < 90 mm/Hg or diastolic blood pressure > 100 or < 50 mmHg 11) patients meeting criteria for orthostatic hypotension at Visit 1 12) significant central nervous system disease including stroke and spinal cord injury within past 6 months 13) current treatment with nitrates, cancer chemotherapy, anti-androgens, or troglitazone and 14) patient's partner currently nursing, pregnant or planning to become pregnant.

**Primary and secondary endpoints: Primary endpoints:** 1) IIEF Erectile Function

Domain (which consists of the sum of Questions 1-5 and 15 of the IIEF) score 2) percentage of "yes" responses to SEP Question 2 (Were you able to insert your penis into the partner's vagina?) and 3) percentage of "yes" responses to SEP Question 3 (Did your erection last long enough for you to have successful intercourse?) For the 3 primary endpoints, the mean change from baseline to endpoint was compared with placebo. Secondary endpoints: include analyses of the Global Assessment Questions, the SEP diary, and the IIEF.

**Withdrawals, compliance, and protocol violations:** The majority of patients (88.4%) completed the trial. One patient in the placebo group, 1 in the IC351 10 mg group and 4 in the IC351 20 mg group discontinued because of an adverse event. These patients are discussed below. The sponsor believes that none of the protocol violations that occurred during this study necessitated a change in the analysis plan or affected the validity of the study results.

**Medical Officer's comment:** The reviewer agrees that the protocol violations did not affect the validity of the study results.

**Efficacy analysis:** IC351, at both 10 and 20 mg, was superior to placebo for all 3 primary endpoints (Table 12).

**Table 12: LVBK Summary of primary efficacy analyses**

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	Placebo (n=71) End (change)	IC351 (10 mg) (n=73) End (change)	IC351 (20 mg) (n=72) End (change)
ED domain of IIEF	12.2 (+0.1)	19.3 (+6.4)*	18.7 (+7.3)*
SEP 2	29.9 (-4.1)	56.7 (+22.2)*	54.4 (+22.6)*
SEP 3	20.0 (+1.9)	48.0 (+28.4)*	41.8 (+29.1)*

\*p<0.001

**Medical Officer's comment:** The changes seen in all 3 primary endpoints are statistically and clinically significant. The mean changes seen with 10 mg and 20 mg IC351 appear similar.

The sponsor believes, based on subgroup analyses, that patients who are more severely affected at baseline or more severely affected by diabetic complications appear to have a greater response to 20 mg than to 10 mg IC351.

**Medical Officer's comment:** The IIEF and SEP questionnaires in the protocol and case report forms are in English. The study was performed in Spain.

The statistical difference between 10 and 20mg may not be clinically significant in most of the severe cases.

### **Safety analysis:**

**Extent of exposure:** The mean number of doses taken per group was 21.6 for the placebo group, 21.0 for the 10 mg group, and 19.3 for the 20 mg group. The mean number of doses taken per week was 1.67, 1.64, and 1.51 for the placebo, 10 mg, and 20 mg IC351 groups, respectively.

### **Serious adverse events:**

No deaths occurred during the study.

Three patients experienced serious adverse events: 1) Patient 104-1414 was diagnosed with bladder cancer. 2) Patient 107-1709 (on placebo) suffered trauma. 3) Patient 117-9706 was diagnosed with prostate cancer.

**Medical Officer's comment:** The reviewer agrees that none of these SAE's was related to study drug.

**Discontinuations due to adverse event:** Six patients discontinued the study because of an adverse event.

Patient 107-1709 experienced trauma and then suffered a myocardial infarction. This patient was randomized to placebo.

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Patient 108-1800 (20 mg IC351) experienced back pain as well as leg and arm pain after his second dose of study drug. The patient elected to withdraw from the study at Visit 3 because of these symptoms. At a follow-up visit several weeks later, this patient also reported that he was experiencing dizziness and vertigo. These symptoms first occurred 42 days after his last dose of study drug and the investigator did not think that these events were related to study drug.

**Medical Officer's comment:**

No further useful information is included in the case report form. The etiology of the back pain is not clear to this reviewer.

Patient 109-1909 (10 mg IC351) experienced neck pain and dyspepsia after his first dose of study drug. He took 5 total doses of study drug. Because of the neck pain and dyspepsia, he withdrew from the trial at Visit 3.

**Medical Officer's comment:** No further useful information is included in the case report form. The patient's pain is described as "cervical."

Patient 112-9202 (20 mg IC351) experienced "blotches" on his face and a headache after a dose of study drug. The symptoms resolved spontaneously on the same day. The patient elected to withdraw from the study after experiencing the same symptoms after a subsequent dose of study drug.

Patient 117-9703 (20 mg IC351) experienced angina 2 days prior to randomization. He did not report this to the investigator. He was hospitalized one day after randomization with a diagnosis of myocardial infarction. He never took a dose of study drug; this was verified by study drug reconciliation.

Patient 117-9717 (20 mg IC351) experienced a headache after his first dose of study drug. The headache was relieved by acetaminophen. The patient elected to withdraw from the study because of the headache.

One other patient (105-1514) had an event classified as "clinically significant but non-serious." This patient (20 mg IC351) had a history of retinal disease and prior to enrollment had been scheduled for elective vitrectomy. Prior to undergoing the procedure the patient suffered a vitreous hemorrhage in his right eye. The investigator believed that the event was related to underlying retinal disease and not related to study drug. The patient continued in the study.

**Medical Officer's comment:** The reviewer agrees that the vitreous hemorrhage was probably not related to study drug.

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### Frequent adverse events:

The most common treatment-emergent adverse events were dyspepsia and headache (Table 13).

**Table 13: LVBK. Adverse events occurring in >4% in any treatment group**

	Placebo (n=71)	IC351 10 mg (n=73)	IC351 20 mg (n=72)
Dyspepsia	0	8 (11%)	8 (11.1%)
Headache	2 (2.8%)	7 (9.6%)	6 (8.3%)
Myalgia	1 (1.4%)	4 (5.5%)	3 (4.2%)
Flu syndrome	3 (4.2%)	3 (4.1%)	3 (4.2%)
Back pain	1 (1.4)	1 (1.4%)	4 (5.6%)

Vasodilation occurred in 0%, 2.7%, and 4.2% of the patients in the placebo, 10 mg and 20 mg groups, respectively. No abnormalities of color vision were reported. One case of right eyelid edema was reported.

### Changes in laboratory values:

Criteria for clinically significant changes in laboratory values were not established a priori in this trial. Clinically relevant laboratory changes were determined by each investigator. Statistically significant differences among treatment groups were observed in the mean change from baseline to endpoint in uric acid and alkaline phosphatase and in the mean change from baseline to maximum in blood glucose.

**Medical Officer's comment:** Although statistically significant, these changes were small and not clinically significant.

### Vital signs:

The mean change in systolic blood pressure (sitting) was -2.97, -4.61, and -0.88 mmHg in the placebo, 10 mg, and 20 mg groups, respectively. Heart rate mean changes were 0.42, -1.18, and 0.67 in the placebo, 10 mg, and 20 mg groups, respectively.

### Medical Officer's overall assessment of efficacy and safety:

Both 10mg and 20 mg showed clinical and statistical significance in improvement of ED.

No deaths were reported. There were no directly attributable SAE's.

Both doses showed satisfactory tolerability profile.

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### 8.4.4. Clinical Trial H6D-MC-LVCO (PI-10mg-20mg)

("A Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of IC 351 (LY450190) Administered "On Demand" to Patients with Erectile Dysfunction") (Trial start October 23, 2000; Trial completion February 22, 2001)

**Objectives: Primary objectives:** 1) to evaluate the efficacy of IC351 at doses of 10 mg and 20 mg, in comparison with placebo, when taken "on demand" over 12 weeks in improving erectile function as measured by the Erectile Function Domain of the IIEF (Questions 1-5 and 15), Question 2 of the Sexual Encounter Profile (SEP) diary, and Question 3 of the SEP diary and 2) to determine the safety of IC351 in men in Taiwan with ED.

Secondary objective: to evaluate the efficacy of IC351 in comparison with placebo in men with ED using other variables including responses to the Global Assessment Questions, the SEP diary, and the IIEF, including questions 3 and 4.

**Design and conduct summary:** The study was a multi center (8 sites in Taiwan), randomized, double-blind, placebo-controlled, parallel design trial to evaluate the safety and efficacy of intermittent "on demand" dosing of two different doses of IC351 or placebo administered for 12 weeks to men in Taiwan with ED. The study population consisted of men at least 21 years of age who reported at least a 3 month history of erectile dysfunction with a range of severity (mild to severe) and etiological classification (psychogenic, organic, and mixed psychogenic and organic). One hundred ninety-seven patients were randomized (10 mg - 65 patients; 20 mg - 65 patients; and placebo - 66 patients).

The study consisted of 2 phases. The first phase was a screening and run-in phase which lasted approximately 4 weeks. At visit 1 the patient and his partner signed an informed consent. After the 4 week run-in period, patients returned for visit 2 if they fulfilled inclusion and exclusion criteria. The patients were then randomized to placebo or 10 or 20 mg of study drug. They then entered a treatment phase which lasted 12 weeks. Patients were evaluated at each month of the 12 week treatment period (Visits 3, 4, and 5). The IIEF and SEP were administered at Visit 2 (baseline), Visits 3 and 4 (interim analysis), and Visit 5 (end of treatment). Vital signs and clinical laboratory analyses were performed at each visit. ECG's were performed at visits 1 and 5. The pharmacokinetics of IC351 was determined in a subset of patients (approximately 25 in each treatment arm).

**Study population:** The study population was men at least 21 years of age who reported at least a 3 month history of erectile dysfunction. Study population baseline characteristics are shown in Table 14.

**Table 14:LVCO Baseline characteristics of randomized patients.**

	Placebo (n=66)	IC351 (10 mg) (n=65)	IC351 (20 mg) (n=65)

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Age (mean)	60.2	59.0	60.4
% Asian	100	100	100
IIEF ED domain (mean)	15.55	14.42	16.95

### **Inclusion and exclusion criteria:**

Inclusion criteria included: 1) men at least 21 years of age 2) history of ED for at least 3 months prior to visit 1 3) made at least 4 sexual intercourse attempts during the 4 week run-in period without medication.

Exclusion criteria included: 1) ED caused by untreated endocrine disease 2) history of radical prostatectomy (with the exception of bilateral nerve-sparing prostatectomy) 3) history of penile implantation 4) evidence of clinically significant renal insufficiency 5) evidence of clinically significant hepato-biliary disease (SGOT or SGPT > 3 x ULN) 6) hemoglobin A1c >13% 7) patients with chronic stable angina treated with long acting nitrates or patients with chronic stable angina who have required short-acting nitrates in the prior 90 days 8) unstable angina within prior 6 months, history of myocardial infarction or coronary artery bypass graft surgery within 90 days or percutaneous coronary intervention within 90 days 9) supraventricular arrhythmia with an uncontrolled ventricular response (HR > 100 bpm) at rest despite medical therapy, history of sustained ventricular tachycardia (HR > 100 bpm for > 30 seconds) despite medical therapy, presence of internal cardioverter-defibrillator 10) congestive heart failure within 6 months 11) new, significant cardiac conduction abnormality within 90 days 11) systolic blood pressure > 170 or < 90 mm/Hg or diastolic blood pressure > 100 or < 50 mm/Hg 12) significant central nervous system disease within past 6 months 13) current treatment with nitrates, cancer chemotherapy, or anti-androgens.

**Primary and secondary endpoints: Primary end-points:** 1) IIEF Erectile Function domain, which consists of the sum of questions 1-5 and 15 of the IIEF 2) percentage of "yes" responses to Question 2 of the SEP (Were you able to insert your penis into your partner's vagina?) and 3) percentage of "yes" responses to Question 3 of the SEP (Did your erection last long enough for you to have successful intercourse?). Secondary endpoints: 1) Questions 3 and 4 of the IIEF 2) percentage of "yes" responses to questions 4 and 5 of the SEP and 3) Global Assessment Questions.

**Withdrawals, compliance, and protocol violations:** The majority (93.4%) of patients completed the study. Five patients experienced SAE's; none of these SAE's was thought to be related to study drug by the investigator. One of these patients discontinued because of an SAE (left ear hearing loss in a patient on placebo). Four patients discontinued secondary to clinically significant laboratory abnormalities (all four patients were on IC351). Three of the 4 cases involved transaminases which rose to greater than 3 x ULN. In all 3 cases, the patient had abnormal transaminases prior to receipt of study drug. The sponsor believes that IC351 did not "contribute to these elevated transaminases." These patients are discussed in the safety analysis (laboratory studies section). 2

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The fourth patient had an elevated GGT at baseline and was discontinued shortly after randomization when the sponsor learned of the elevated GGT. There were no significant protocol violations during the study.

### **Efficacy analysis:**

IC351, at both 10 mg and 20 mg, was superior to placebo for all 3 primary endpoints (Table 15).

**Table 15:LVCO. Summary of Primary Efficacy Analyses.**

	Placebo End (change)	IC351 (10 mg) End (change)	IC351 (20 mg) End (change)
ED domain of IIEF	18.1(+2.6)	22.6 (+8.1)*	25.0 (+8.0)*
SEP 2	54.5(+9.5)	76.9 (+34.5)*	84.9 +(35.3)*
SEP 3	42.8 (+14.7)	70.0 (+47.9)*	78.0 (+49.7)*

\* = p<0.001

**Medical Officer's comment:** The mean changes show similar results in the 10 and 20 mg groups. The responses in all the variables were robust as compared to the other trials. This may be due to the lower BMI in this population.

Generally, efficacy was greater in patients who were more severely affected at baseline. Erectile Function Domain score changes for patients with mild ED at baseline were similar between the 10 and 20 mg IC351 groups (0.3 for placebo, 3.0 for the 10 mg IC 351 group, and 3.7 for the 20 mg group). EF domain score changes for patients with moderate and severe ED at baseline were greater in the 20 mg group than in the 10 mg group. Mild, moderate, and severe ED were defined as IIEF ED domain scores of 17-30, 11-16, and 1-10 respectively. ED domain score changes for patients with moderate ED at baseline were 4.3 for placebo, 10.2 for the 10 mg group, and 12.5 for the 20 mg group. ED domain score changes for patients with severe ED at baseline were 4.0 for the placebo group, 12.5 for the 10 mg group, and 14.9 for the 20 mg group. Patients who had moderate or severe ED at baseline appeared to have a greater response to 20 mg than to 10 mg IC351.

**Medical Officer's comment:** The IIEF and SEP questionnaires in the protocol and case report forms are in English. The study was performed in Taiwan. Clinical data for efficacy is notable for robust responses. It is unclear if this data results can be completely extrapolated to the general US population at large .

### **Safety analysis:**

**Extent of exposure:** The mean number of doses taken per group were 37.49 for placebo, 50.89 for the 10 mg group, and 48.55 for the 20 mg group. The mean number of doses taken per week were 2.95 for placebo, 3.92 for the 10 mg group, and 3.66 for the 20 mg group.

### **Serious adverse events:**

No deaths occurred during the study. Five patients experienced serious adverse events. All of these events were judged by the investigator as not being related to study drug.

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One patient treated with placebo suffered a myocardial infarction. One patient on 10 mg IC351 underwent a surgical procedure for chronic rhinitis. He had a long history of rhinorrhea and nasal congestion and had undergone a previous nasal operation. The other 3 SAE's were urinary retention requiring TURP, tooth infection requiring hospitalization, and TUR of a bladder :neck contracture secondary to a previous TURP.

**Medical Officer's comment:** The reviewer agrees that none of the SAE's were drug related.

**Discontinuations due to adverse event:** Five patients discontinued the study because of an adverse event. One patient on placebo discontinued because of a left ear hearing loss. Four patients discontinued because of elevated liver function studies. These patients are discussed below under "laboratory abnormalities."

**Frequent adverse events:** Treatment-emergent adverse events reported for greater than 5% of all patients, or for greater than 5% of patients receiving IC351 were back pain, rhinitis, dyspepsia, infection, myalgia, cough, dizziness, and headache (Table 16).

**Table 16: LVCO Treatment emergent adverse events occurring in >5% of all patients or greater than 5% of patients receiving IC351**

	Placebo N (/o °)	IC351 10 mg N (%)	IC351 20 mg N (%)
Back pain	2(3.0)	7(10.8)	5(7.7)
Dyspepsia	1(1.5)	6(9.2)	6(9.2)
Myalgia	0	6(9.2)	6(9.2)
Infection	4(6.1)	3(4.6)	6(9.2)
Rhinitis	6(9.1)	4(6.2)	4(6.2)
Dizziness	4(6.1)	3(4.6)	4(6.2)
Headache	3(4.5)	3(4.6)	4(6.2)
Cough increased	5(7.6)	3(4.6)	3(4.6)

In the 10 mg IC351 group, back pain was rated by the investigator as mild in 4, moderate in 2, and severe in 1. In the 20 mg group, back pain was rated as mild in all 5 cases. In the placebo group, back pain was rated as mild in 1 and severe in 1.

The incidence of flushing (coded as vasodilation) was 3.0%, 4.6%, and 4.6% in the placebo, 10 mg, and 20 mg IC351 groups, respectively. No abnormalities of color vision were reported.

### **Medical Officers Comments:**

The incidence of Backpain, dyspepsia and myalgia was notably high when compared to the other pivotal studies, while incidence of headache was relatively low.

### **Changes in laboratory values:**

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Criteria for clinically significant laboratory values were not established a priori. Clinically relevant laboratory values were established for each investigator.

There were no clinically significant differences between the three treatment groups with regard to any change in a laboratory parameter, in particular liver function tests and hematology.

Individual patient changes - clinically significant abnormalities:

Five patients experienced clinically significant laboratory abnormalities:

- 1) Patient 803-4168: This man taking 20 mg IC351 discontinued the study secondary to elevated serum transaminases. He had a history of hepatitis B in 1994. At Visit 1, his ALT and AST were normal (31 U/L and 25 U/L, respectively). At Visit 2 (prior to receiving drug), the AST and AST were slightly elevated (62 U/L and 42 U/L respectively). These abnormalities were not deemed clinically significant and the patient was randomized. At Visit 3, the ALT and AST had risen to 192 U/L and 104 U/L. Since the ALT was now >3 times the ULN, the sponsor elected to discontinue this patient from the study. At his early termination visit, his ALT and AST remained elevated at 102 U/L and 59 U/L. The bilirubin was normal at all visits. The patient took study drug a total of 7 times. The investigator believed that the elevated liver enzymes were unrelated to study drug. The enzymes were elevated prior to starting drug and the sponsor believes that the enzymes were likely the result of the patient's history of hepatitis B.

**Medical Officer's comment:** The elevated transaminases may well be due to the patient's history of hepatitis B. A possible role of IC351 can not be totally excluded.

- 2) Patient 802-4100: This man taking 10 mg IC351 was discontinued from the study secondary to elevated serum transaminases. He had no significant past medical history except for the consumption of 21 "units of alcohol" per week. Laboratory values at screening showed an elevated GGT (123 U/L), ALT (102 U/L), AST (93 U/L) and a normal bilirubin (13umol/L). Because these values were not deemed to be clinically significant, the patient was randomized. At Visit 2 (prior to receiving study drug), he had elevated GGT (86 U/L), ALT (110 U/L), and AST (120 U/L) and a normal bilirubin. Between Visits 2 and 3 the patient took study drug almost daily. At Visit 3, GGT, ALT, and AST had decreased but remained abnormal (62 U/L, 67 U/L, and 80 U/L, respectively). Between Visits 3 and 4, the patient took study drug regularly and his alcohol consumption rose from 21 to 60 units/week. At Visit 4, the GGT, ALT, and AST were 155, 114, and 160 U/L, respectively. His bilirubin remained normal. Because his AST was > 3 x UNL, he was discontinued by the sponsor. Three weeks after the last dose of study drug, his GGT, ALT, and AST were 172, 209, and 264 U/L, respectively. He was referred to a hepatologist, but the patient refused further follow-up. The investigator believed that the liver enzyme abnormalities were unlikely to be related to

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study drug. The liver enzyme abnormalities were present prior to receiving study drug and were thought to be related to the patient's alcohol consumption.

**Medical Officer's comment:** The elevated transaminases were likely secondary to the patient's alcohol consumption.

3) Patient 803-4150: This man was randomized to 10 mg IC351 and was discontinued because of GGT elevation. He had an elevation of GGT at Visit 1 and 2 (224 U/L and 307 U/L, respectively) prior to receiving study drug. His ALT and AST were normal at both visits. At screening, he reported an

alcohol intake of 2 "units" per week and no concomitant medications. The sponsor deemed the GGT elevation to be clinically significant and the patient was discontinued shortly after randomization. He took 4 doses of study drug prior to discontinuation. At his termination visit, his GGT remained unchanged at 224 U/L.

**Medical Officer's comment:** The GGT remained unchanged during the study.

4) Patient 805-4261: This patient received 20 mg IC351 and had changes in his BUN (10.3 nmol/L to 14.0 nmol/L), creatinine 133 umol/L to 184 umol/L) and hemoglobin (119 g/L to 91 g/L) between visits 3 and 4. His medical history was significant for diabetes, hypertension, hepatitis C, and BPH. He had mild renal insufficiency at baseline (creatinine 135 umol/L). He was also slightly anemic at baseline (hemoglobin at Visits 1 and 2 of 124 g/L and 111 g/L). The patient had discontinued his diabetes and hypertension drugs 14 days prior to his Visit 4 blood draw. After resuming these medications, the patient's BUN and creatinine had fallen to their baseline values. The patient remained anemic and he was referred for evaluation. He was diagnosed as having a duodenal ulcer. The investigator speculated that his ulcer may have been due to concomitant drugs (including aspirin); he was unable to rule out a relationship to study drug. The patient took study medication 25 times during the study and remained in the study and completed the protocol.

**Medical Officer's comment:** The hematology laboratory abnormalities were likely due to the patient's ulcer.

5) Patient 805-4269: This patient received 10 mg IC351 and discontinued the study because of elevated serum transaminases. He had a history of hepatitis C diagnosed in 1988. At screening, his ALT and AST were elevated (58 and 57 U/L, respectively). These values had risen to 121 U/L and 84 U/L at visit 2 (prior to receiving study drug). The values were not considered exclusionary and the patient was randomized. At visit 3, the ALT and AST were both greater than 3 x ULN (165 and 123 U/L, respectively). He was discontinued. His bilirubin was normal at all visits. He took 21 doses of study drug. The sponsor believes that the enzyme abnormalities are likely due to the patient's chronic hepatitis C.

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### **Medical Officer's comment:**

The transaminase elevations are probably due to the patient's hepatitis. An effect of IC351 on the transaminases can not be totally excluded.

Vital signs: There was no clinically significant change in heart rate or blood pressure in the placebo or drug groups.

### **Medical Officer's assessment of efficacy and safety:**

In the opinion of this reviewer, the efficacy data presented in Trial LVCO support the efficacy of IC351(10mg and 20mg) for the treatment of erectile dysfunction. However there were some note worthy differences; Robust responses may be due to relatively lower BMI in this trial. Higher incidence of back pain, dyspepsia and myalgia while a relative lower incidence of headache.

No deaths were reported and no attributable SAE's were reported.

### **8.4.5 Clinical Trial : STUDY LVDJ: (PI-10mg-20mg)**

**Title:** A Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of IC351 (LY450190) Administered "On Demand" to Patients with Erectile Dysfunction.

(Study dates:10-25-2000 to 4-02-2001)

**Objectives:** **Primary objectives:** 1) to evaluate the efficacy of IC351 at doses of 10 mg and 20 mg, in comparison with placebo, when taken "on demand" over 12 weeks in improving erectile function as measured by the Erectile Function Domain of the IIEF (Questions 1-5 and 15), Question 2 of the Sexual Encounter Profile (SEP) diary, and Question 3 of the SEP diary and 2) to determine the safety of IC351 in men in Canada with ED. **Secondary objective:** to evaluate the efficacy of IC351 in comparison with placebo in men with ED using other variables including responses to the Global Assessment Questions, the SEP diary, and the IIEF, including questions 3 and 4.

**Study Design :** This was a multi-center (25 sites in Canada), randomized, double-blind, placebo-controlled, parallel design study. The study population consisted of men at least 18 years of age who had a monogamous relationship with a female sexual partner and a history of erectile dysfunction (ED) at least 3 months in duration. Individuals presenting with ED with a functional severity between mild and severe and with any etiological classification (psychogenic, organic, or mixed) were eligible for enrollment. The subjects were randomized in the following manner: 20 mg IC351 100 ; 10 mg IC351: 103; Placebo: 50. Table 17 shows the schedule of events for sudy LVDJ.

**Table 17: LVDJ: Schedule of events:**

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Week	-4	0	4	8	12
(Study days)*	(-35 to -28)	(0)	(28 to 35)	(28 to 35)	(28 to 35)
			days after Visit 2)	days after Visit 3)	days after Visit 4 or early discontinuation)
Visit	1	2	3	4	5
Activity					
Patient Informed Consent	X				
Partner Informed Consent	X				
Randomization		X			
Medical History	X				
Vital Signs (BP, HR)	X	X	X	X	X
Physical Examination	X				X
12-lead ECG	X				X
Height	X				
Weight	X				
Clinical Chemistry, Hematology	X	X	X	X	X
Urinalysis	X				X
Plasma IC351 Concentrations			X	X	X
Administration of IIEF		X	X	X	X
SEP Diary Dispensed	X	X	X	X	
SEP Diary Review/CRF transfer		X	X	X	X
Global Assessment Questions					X
Study drug dispensing		X	X	X	
Study drug reconciliation			X	X	X
Concomitant medications	X	X	X	X	X
Adverse events		X <sup>d</sup>	X	X	X

### **Demographic and Other Baseline Characteristics.**

The mean age was 59.1 years in the 20-mg IC351 group, 58.3 years in the 10-mg IC351 group, and 58.5 years in the placebo group. The number of patients who were Caucasian was 95 (95.0%) in the 20-mg IC351 group, 98 (95.1%) in the 10-mg IC351 group, and 48 (96.0%) in the placebo group. The most common etiology of erectile dysfunction (ED) was organic, accounting for 54 (54.0%) in the 20-mg IC351 group, 65 (63.1%) in the 10-mg IC351 group, and 30 (60.0%) in the placebo group. The mean IIEF Erectile Function Domain score at baseline was 15.1 in the 20-mg IC351 group, 14.6 in the 10-mg IC351 group, and 15.0 in the placebo group. All other demographic characteristics were well balanced among the IC351 and placebo groups.

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### **Medical Officers Comments:**

These demographic characteristics are similar to the other studies.

### **Treatment Compliance**

The dosing regimen for this study was as needed, requiring no formal measure of compliance. The maximum dosing frequency allowed during the study was one dose daily. Patients were asked to return all used and unused study medication blister packs. Patients were to enter all doses taken in a patient diary (Sexual Encounter Profile), which were reconciled with the returned blister packs. Site personnel reviewed returned blister cards to ensure that patients took a full (two-tablet) dose when taking the study medication. Accountability records were maintained at Visits 3, 4, and 5.

### **Protocol Violations**

Significant protocol violations are defined as deviations from the protocol that could have had an impact on patient safety, data integrity, or conclusions drawn from the study.

**Table 18 LVDJ: Summary of Significant Protocol Violations by Site(source Table LVDJ.10.3)**

Significant Protocol Violation	Site
Inclusion/exclusion violation	003, 004, 005, 006, 010, 015, and 024
Drug accountability violation	004, 008, 006, and 024
Informed Consent violation	015

### **Medical Officers Comments:**

These protocol violations should not affect the validity of the study, analysis and conclusions drawn from its results.

### **Efficacy Evaluations:**

Both 10mg and 20 mg significantly ( $p < .001$ ) improved ED parameters when compared with placebo .

The primary and secondary end points were met .Table 19

**Table 19 :LVDJ ,Efficacy evaluations:(source Table LVDJ. 11. 2.)**

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	All (N=253)	Placebo (N=50)	IC 10mg (N=103)			IC 20mg (N=100)		
	BASE	END CHG	END	CHG	P	END	CHG	P
IIEF Domains								
Erectile Function	15.0	14.5-0.9	21.2	6.6	<.001	23.3	8.0	<.001
Patient SEP Questions								
2. Insert Penis into Vagina	52.7	45.3-6.4	72.5	21.3	<.001	76.0	21.3	<.001
3. Successful Intercourse	27.9	31.9-4.9	56.7	32.8	<.001	61.5	29.0	<.001

**Medical Officer's comment:** The mean changes show similar results in the 10 and 20 mg groups. 10mg dose did better in SEP 3 while 20mg was superior in IIEF.

**Safety evaluation:**

**Exposure To Study Drug:**

The patient mean doses per week was 2.38, 2.04, 2.12 for placebo, 10mg and 20 mg respectively. Table 20:

**Table 20 :Exposure to study drug (Source Table LVDJ.12.1.)**

Variable	Placebo (N=50)	IC 10 mg (N=103)	IC 20 mg (N=100)
Mean Doses / Week			
No. Patients	50	103	100
Mean	2.38	2.04	2.12
Median	1.91	1.69	1.70
Standard Dev.	1.48	1.35	1.42

**Adverse events:**

Most frequent adverse are shown in Table 21.

**Table 21 : LVDJ: Treatment Emergent Adverse Events (Table LVDJ. 12. 2.)**

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Event Classification	Placebo N=50	IC 10mg N=103	IC 20mg N=100
DYSPEPSIA	1 (2.0)	10 (9.7)	22 (22.0)
HEADACHE	4 (8.0)	15 (14.6)	17 (17.0)
INFECTION	11 (22.0)	20 (19.4)	11 (11.0)
PAIN	1 (2.0)	10 (9.7)	8 (8.0)
FLU SYNDROME	5 (10.0)	8 (7.8)	5 (5.0)
BACK PAIN	1 (2.0)	5 (4.9)	7 (7.0)
RHINITIS	2 (4.0)	6 (5.8)	4 (4.0)
VASODILATATION	2 (4.0)	4 (3.9)	6 (6.0)
MYALGIA	2 (4.0)	5 (4.9)	4 (4.0)
ACCIDENTAL INJURY	2 (4.0)	1 (1.0)	5 (5.0)
COUGH INCREASED	3 (6.0)	3 (2.9)	2 (2.0)
SURGICAL PROCEDURE	1 (2.0)	4 (3.9)	1 (1.0)

**Medical Officer's comment:**

Headache and dyspepsia occurred in 17% and 22% of the patients respectively in 20mg dose group and 14.6% and 9.7% in 10 mg. Headache and dyspepsia appeared to be dose related.

**Vital signs and Labartory Values.**

The heart rate systolic BP and diastolic BP did not show significant changes post treatment. SBP was notable for a mean drop of 2-3 mmHg. No clinically significant Lab values were noted.

**Medical Officer's comment:**

Vital signs: There was no clinically significant change in heart rate or blood pressure in the placebo or drug groups except SBP was notable for a mean drop of 2-3 mm/ Hg.

Lab abnormalities (hematology and chemistry including LFT's) could not be directly attributed to IC351.

**Study Discontinuation analysis:** This multi -center trial enrolled 253 patients. The majority (86.6%) of patients completed this study. Five patients (2.0%) discontinued due to an adverse event. Table 22 :

**Table 22:LVDJ ;Discontinuations (Table LVDJ. 10. 2.)**

	Placebo	IC 10mg	IC 20mg	Total
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Status	(N=50)	(N=103)	(N=100)	(N=253)
	n (%)	n (%)	n (%)	n (%)
Protocol completed	44 (88.0)	89 (86.4)	86 (86.0)	219 (86.6)
Adverse event	0	2 (1.9)	3 (3.0)	5 (2.0)
Lack of efficacy, patient perception	2 (4.0)	2 (1.9)	0	4 (1.6)
Unable to contact patient (lost to follow-up)	1 (2.0)	0	0	1 (0.4)
Personal conflict or other patient decision	2 (4.0)	5 (4.9)	7 (7.0)	14 (5.5)
Protocol entry criteria not met	0	1 (1.0)	0	1 (0.4)
Physician decision	0	1 (1.0)	0	1 (0.4)
Protocol Violation	1 (2.0)	3 (2.9)	4 (4.0)	8 (3.2)

### Deaths , Serious Adverse Events:

There were no deaths in the study.

There was one serious AE : angina pectoris occurring in a pt 2152, site 24 Patient 024-2152, who received treatment with 10 mg of IC351, was admitted to hospital on \_\_\_\_\_, due to unstable angina. He was discharged from the hospital on \_\_\_\_\_ with a Nitrospray, Aspirin, Cardizem, Losec and a Nitrodur patch. The patient was then seen for his study Visit 2 on \_\_\_\_\_. The patient did not tell the site staff that he had been in hospital, or that he had angina and was taking nitrates. The patient was subsequently randomized. The patient then called the site on \_\_\_\_\_ indicating that he did not want to be in the study and that his wife had thrown away his study medication and diaries. The patient refused to come into the office for the study-discontinuation procedures. The investigator reported this event as unrelated to study drug.

### The following summarizes the adverse events:

Patient 003-1110, who received treatment with 20 mg of IC351 was discontinued due to the diagnosis of angina pectoris. His pre-randomization examinations were normal with the exception of a high blood pressure of 172/96 and the patient was randomized by the site without Sponsor approval. The patient has a history of hypertension and diabetes mellitus. The patient returned prior to his scheduled Visit 3 to discontinue from the study after taking 8 doses of IC351. At that time the site personnel learned that the patient had been experiencing chest pain since \_\_\_\_\_ (prior to randomization) and had been recently diagnosed with angina pectoris by a cardiologist. He was advised to

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start treatment with aspirin, diltiazem and nitrolingual spray. The patient reported taking study drug up to \_\_\_\_\_ but has stated that he was not using his nitrates during that time. The investigator reported this event as unrelated to study drug.

Patient 004-1171, who received treatment with 10 mg of IC351, discontinued the study due to the dyspepsia that he experienced when taking IC351. Of note, the patient was taking indomethacin for gout. The dyspepsia started after the first dose of study drug and continued for approximately a week after his last dose of IC351. The patient did not report any other events and sent a letter to the site dated \_\_\_\_\_ to indicate that he did not wish to participate in the study. The patient refused to come back to the site at the time of discontinuation, resulting in no early-discontinuation procedures being conducted. The investigator reported these events as related to study drug.

Patient 008-1370, who received treatment with 20 mg of IC351, experienced intermittent increases in his heart rate between \_\_\_\_\_. These symptoms started with the first dose of IC351 and ended after the 12th dose of IC351. The patient went on to take an additional 14 doses of study drug without further incident. The patient has a history of intermittent chest pain since 1965 and has had a mitral valve prolapse since 1991. The study investigator reported this event as related to study drug, and the patient remained in the study and completed the protocol.

Patient 011-1504, who received treatment with 10 mg of IC351, experienced two to three occurrences of mild heart thumping from \_\_\_\_\_.

The patient experienced the first episode of heart thumping after his first dose of IC351. The patient told the study site staff that the symptoms were not severe and, as such, the patient never sought out medical attention. The patient took a total of 6 doses of IC351 during the time that he reported experiencing the heart thumping. The patient went on to take 15 additional doses of IC351 without a reoccurrence of these symptoms. The patient has a history of experiencing these symptoms while taking Viagra. The study investigator reported these events as related to study drug. However, in the Sponsor's opinion, a strict causal relationship cannot be established as the patient was symptom-free after the intake of 15 additional doses. However, in the Sponsor's opinion, a strict causal relationship cannot be established as the patient was symptom-free after the intake of 14 additional doses.

Patient 018-1851, who received treatment with 20 mg of IC351, indicated that he lost consciousness while standing in the aisle of a plane waiting to use the washroom, after drinking a double scotch and a glass of wine. After the episode, the patient was examined by medical personnel, who reported no obvious abnormality or diagnosis. This syncopal episode occurred two days after the patient's first dose of IC351. The patient has indicated that he has a history of fainting. The patient went on to take an additional 14 doses of study medication without incident. The investigator has ruled this event as not related to study drug.

Patient 019-1900, who received treatment with 20 mg of IC351, experienced dizziness

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while taking his 11th dose of IC351. The patient went on to take 11 more doses of IC351 with the same experience. This patient suffers from arthritis, hyperlipemia, and hypertension. He experienced headache and dizziness while on the study and experienced the flu, which ended 13 days prior to the onset of dizziness. The investigator has reported this event as related to study drug. However, in the Sponsor's assessment, it is difficult to establish a causal relationship given the fact that the patient had taken 10 doses without incident.

Patient 023-2103, who received treatment with 20 mg of IC351, experienced a "fuzzy feeling" or lightheadedness after taking his first dose of study drug and after every dose that he took during the study. The patient took a total of 16 doses of IC351. This patient has a history of diabetes, gout, hyperlipemia, abnormal liver function tests, and parathyroid disorder. The patient also experienced dyspepsia, cholelithiasis, a kidney calculus, and liver fatty deposits while on study. The fatty deposits in the liver were attributed by the investigator to the patient's hyperlipemia and weight. The investigator has ruled dizziness as related to study drug.

### **Medical Officer's assessment of efficacy and safety:**

In the opinion of this reviewer, the efficacy data presented in Trial LVDJ support the efficacy of IC351 (10mg and 20mg) for the treatment of erectile dysfunction. The 20mg and 10mg showed similar efficacies.

No deaths were reported. No directly attributable SAE's were reported. Headache and dyspepsia showed a slight dose related increase.

### **8.4.6 Clinical Trial : Study LVCQ ( PI - 20mg)**

**Title: A Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of IC351 (LY450190) Administered Over 3 Months "On Demand" to Patients with Erectile Dysfunction (Dates of Study: 12 September 2000 through 16 February 2001 (last 3-month patient visit)).**

**Objectives: Primary objectives:** 1) to evaluate the efficacy of IC351 20 mg, in comparison with placebo, when taken "on demand" over 12 weeks in improving erectile function as measured by the Erectile Function Domain of the IIEF (Questions 1-5 and 15), Question 2 of the Sexual Encounter Profile (SEP) diary, and Question 3 of the SEP diary and 2) to determine the safety of IC351 in men in Australia with ED. Secondary objective: to evaluate the efficacy of IC351 in comparison with placebo in men with ED using other variables including responses to the Global Assessment Questions, the SEP diary, and the IIEF, including questions 3 and 4.

**Study Design and conduct :** The study was a multicenter (4 sites in Australia), randomized, double-blind, placebo-controlled, parallel design trial to evaluate the safety and efficacy of intermittent "on demand" dosing of 20mg of IC351 or placebo

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administered for 12 weeks to men in Australia with ED. The study population consisted of men at least 21 years of age who reported at least a 3 month history of erectile dysfunction with a range of severity (mild to severe) and etiological classification (psychogenic, organic, and mixed psychogenic and organic). One hundred and forty patients were randomized (20 mg - 93 patients; and placebo - 47 patients).

The study consisted of 2 phases. The first phase was a screening and run-in phase which lasted approximately 4 weeks. At visit 1 the patient and his partner signed an informed consent. After the 4 week run-in period, patients returned for visit 2 if they fulfilled inclusion and exclusion criteria. The patients were then randomized to placebo or 20 mg of study drug. They then entered a treatment phase which lasted 12 weeks. Patients were evaluated at each month of the 12 week treatment period (Visits 3, 4, and 5). The IIEF and SEP were administered at Visit 2 (baseline), Visits 3 and 4 (interim analysis), and Visit 5 (end of treatment). Vital signs and clinical laboratory analyses were performed at each visit. ECG's were performed at visits 1 and 5. The pharmacokinetics of IC351 was determined in a subset of patients (approximately 25 in each treatment arm).

### Disposition of Patients

This ongoing multicenter trial enrolled 140 patients. The majority, 125 (89.3%), of patients completed the study through Visit 5. Of the placebo patients, 8.5% discontinued due to a perceived lack of efficacy. Of the IC351- treated patients, 3.2% discontinued due to a perceived lack of efficacy while 4.3% discontinued due to an adverse event.

### Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics (except age) did not differ significantly between the two treatment groups. Although age was statistically significant between the placebo group and the IC351 group, it was not clinically meaningful. The characteristics summarized are age, ethnicity, weight, height, etiology and duration of erectile dysfunction, IIEF Erectile Function Domain severity, smoking status, current alcohol consumption, and amount of alcohol consumed.

The mean age was 61.3 years in the placebo group and 58.2 years in the IC351 group. The number of patients who were Caucasian was 46 (98%) in the placebo group and 91 (98%) in the IC351 group. The most common etiology of ED was mixed, accounting for 24 patients (51%) in the placebo group and 46 patients (50%) in the IC351 group. The second most common etiology of ED was organic, accounting for 21 patients (45%) in the placebo group and 37 patients (40%) in the IC351 group. The mean IIEF Erectile Function Domain score at baseline was 14.3 in the placebo group and 16.2 in the IC351 Group. All other demographic characteristics were well balanced between the IC351 and placebo treatment groups.

**Efficacy Results:** The 20 mg dose was effective in the treatment of ED population studied. Table 23

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**Table 23:LVCQ, Efficacy results (Source Table LVCQ. 11. 2.)**

	All (N=140)	Placebo (N=47)	IC 20mg (N=93)			
	BASE	END	CHG	END	CHG	P
<b>IIEF Domains</b>						
Erectile Function	15.4	13.0	-1.3	23.7	7.7	<.001
<b>Patient SEP Questions</b>						
2. Insert Penis into Vagina	53.0	42.4	-7.2	81.3	26.5	<.001
3. Successful Intercourse	30.8	26.2	0.4	74.1	40.7	<.001

**Medical Officers Comments:**

The 20 mg dose showed a significant improvement in ED

**Safety evaluations:**

**Drug Exposure**

Patients were randomized to treatment as follows: 47 to placebo and 93 to 20 mg IC351. Patients on placebo took an average of 2.35 doses per week and patients on 20 mg IC351 took an average of 2.0 doses per week.

**Adverse Events**

The most common treatment-emergent adverse events were headache, dyspepsia, and back pain. No abnormalities of color vision were reported.

**Treatment-Emergent Adverse Events**

A treatment-emergent adverse event is defined as a condition not present at baseline that appeared post base line, or a condition present at baseline that increased in severity post base line. Of the placebo patients, 72.3% had treatment-emergent adverse events, whereas 81.7% of IC351 patients had treatment-emergent adverse events. There was no significant difference between the two treatment groups with regard to the overall incidence of treatment-emergent adverse events (p=0.275).

Headache occurred in 34 patients (36.6%) in the IC351 treatment group and in 3 patients (6.4%) in the placebo group. Dyspepsia was reported in 17 patients (18.3%) in the IC351 treatment group and was not reported in the placebo group. There was a statistically significant difference between the IC351 treatment group and the placebo group in the incidence of headache (p=0.001) and dyspepsia (p=0.001). See Table24:

**LVCQ (3- Month Analysis; source LVCQ. 12. 2)**

**Table 24:LVCQ Treatment- Emergent Adverse Events**

Placebo (N=47)	IC 20mg (N=93)