dysfunction are many times statistically significant but when reported as their component parts do not reach the level of >5%. The following table illustrates these events.

Table C-5.F.1 Spontaneous Reports of Sexual Dysfunction in Placebo Controlled Studies of Duloxetine

Adverse Events	Placebo (N=723)		Duloxetine (N=1032)		P-value Fishers Exact Test(2 Tail)	P-value for CMH General Association
	n	(%)	n	(%)		
Libido decreased	5	(0.7)	32	(3.1)	<.001	<.001
Anorgasmia	0	(0.0)	25	(2.4)	<.001	<.001
Ejaculation failure	2	(0.3)	14	(1.4)	.020	.024
Erectile disturbance	2	(0.3)	11	(1.1)	.087	.035
Ejaculation disorder NOS	1	(0.1)	7	(0.7)	.151	.085
Orgasm abnormal	4	(0.6)	7	(0.7)	1.00	.557
Sexual dysfunction NOS	0	(0.0)	7	(0.7)	.046	.017

Since spontaneous reporting usually under estimates the rates at which sexual dysfunction occurs, the sponsor inquired systematically during blinded treatment using the Arizona Sexual Experience Questionnaire (ASEX) in studies HMAQ and HMAT (a and b).

Results of the ASEX seem to suggest that male sexual function is more effected than female. Total ASEX score increased by a mean of 1.5 (SD 4.4, p=0.02) in men taking duloxetine versus –0.04 in men taking placebo. There was no difference in the placebo versus duloxetine treated female patients mean total ASEX score. Analysis by item shows a significant difference on item 4 for men -achieving orgasm(duloxetine treated men had an increase of 0.7 versus 0.0 for placebo treated men [SD1.3, p=<0.001]). A more useful analysis to estimate the numbers of patients with changes in sexual function might be the percentage of patients (sub-divided by sex) who experienced a 2 point increase in score on any item of the ASEX from baseline to end of treatment.

C-5.G Analysis of Hepatic Analytes

The overall animal toxicology data indicates that the liver is the organ of toxicity for duloxetine; however, organ histology did not show signs of hepatic necrosis. Because of this the sponsor specifically searched for perturbations in hepatic analytes in the clinical setting.

An enzyme surveillance program was implemented to allow prompt identification of clinically meaningful hepatic enzyme change, with subsequent clinical follow up and historical data gathering for each patient. The sponsor employed three levels of stringency. First, all instances of ALT elevations ≥2X upper limit of normal or AST ≥500 U/L were summarized in one-page patient summaries. Second, additional laboratory limits assessed treatment-emergent values of all relevant hepatic analytes that exceeded PCS levels. Finally, the least stringent threshold

examined those values exceeding the Lilly reference ranges for any analyte, or exceeding pre-specified relative increases from an individual patient's baseline value for selected analytes. Cross tabulation was also performed to determine whether any abnormal transaminase elevation was associated with a concurrent abnormal elevation in bilirubin or jaundice.

Central Tendency of Hepatic Analytes

Mean changes in AST, ALT, and alkaline phosphatase (ALKPH) were significantly higher than placebo. Changes in GGT and total bilirubin were not. Table C-5.G.1 enumerates these changes.

Table C-5.G.1 Hepatic Analytes Mean Change from Baseline to Endpoint, by Dose Placebo-Controlled Integrated Primary Safety Database

Lab Test-Units		Baseline			Change to Endpoint			
	Therapy	n	Mean	SD	Mean	SD	Therapy	Pair-wise
AST- U/L	Placebo	668	22.18	8.24	0.00	9.99	<.001	
	Dlx20bid	294	21.51	7.89	2.91	10.24	(.195)	<.001
	Dlx60qd	225	25.20	12.24	0.23	14.09		.727
	Dlx40bid	286	21.81	11.74	1.35	8.01		.002
	Dlx Forced titration	145	22.10	7.01	1.71	8.24		.009
ALT- U/L	Placebo	668	23.03	14.18	-0.54	11.86	<.001	
	Dlx20bid	294	22.31	13.24	4.28	19.31	(.141)	<.001
	Dlx60qd	225	26.26	16.39	-0.77	14.06		.801
	Dlx40bid	286	23.09	18.10	2.15	11.43		<.001
	Dlx Forced titration	145	25.80	15.54	1.41	14.91		.111
ALKPH- U/L	Placebo	668	68.3	18.7	-0.8	9.6	<.001	
	Dlx20bid	294	68.9	21.0	2.6	11.6	(.593)	<.001
	Dlx60qd	225	73.3	19.7	-0.2	10.1		.007
	Dlx40bid	286	68.5	20.2	2.3	10.5		.004
	Dlx Forced titration	145	68.2	20.1	1.4	8.5		.108
GGT- U/L	Placebo	668	24.54	23.27	0.15	16.74	.359	
	Dlx20bid	294	24.20	21.16	0.16	16.54	(.895)	.896
	Dlx60qd	225	28.60	33.21	-3.10	17.52		.050
	Dlx40bid	286	23.55	19.64	0.02	9.23		.581
	Dlx Forced titration	145	25.83	18.35	-2.86	9.75		.928
T.BILI umol/L	Placebo	655	7.6	4.3	0.1	3.4	.250	
	Dlx20bid	294	7.5	4.2	-0.1	3.3	(.120)	.289
	Dlx60qd	225	6.6	3.3	0.2	2.6		.255
	Dlx40bid	286	7.2	4.1	-0.4	2.8		.051
	Dlx Forced titration	138	8.6	4.5	-0.3	2.9		.614

From NDA 21-427 table ISS.4.2.1

Outliers with Respect to Hepatic Analytes

There is virtually no change in mean hepatic analyte values in the labs that were drawn 14-days after discontinuation of double blind treatment.

Two patients dropped out due to elevated liver function tests (LFT). Neither patient became jaundiced or had an abnormal total bilirubin. Both patients exhibited a similar pattern of LFT elevation GGT approximately 2-7 times normal, ALT approximately three times normal, and AST no more than 1.5 times normal. Both patients had labs return to normal after the drug was discontinued; neither patient had positive work-ups for gall bladder disease or infectious hepatitis. This pattern is consistent with hepatic steatosis that most commonly occurs in association with heavier alcohol use and may be associated with drug hepatotoxicity.

Table C-5.G.2 shows the incidence of PCS hepatic analytes in the placebo controlled primary database. CPK reaches significance; however, ALT, AST, GGT, ALKPH, and total bilirubin do not. The only case of PCS elevated total bilirubin was a placebo treated patient.

Table C-5.G.2 Incidence of PCS Hepatic Analytes in Primary Placebo Controlled Database

		DULOXETINE			PLACEBO			Fisher's Exact
Analyte	Abnormality	N	n	Percent	N	n	Percent	P-value
CPK	HIGH	942	15	1.6 %	656	4	0.6 %	.100
GGT	HIGH	945	2	0.2 %	663	2	0.3 %	1.000
ALT	HIGH	949	2	0.2 %	667	0	0.0 %	.515
AST	HIGH	949	1	0.1 %	667	0	0.0 %	1.000
T.BILI	HIGH	942	0	0.0 %	653	1	0.2 %	.409
ALKPH	HIGH	950	0	0.0 %	668	0	0.0 %	

In the analysis of treatment-emergent abnormal values for hepatic analytes at anytime during the study, there was a significant difference for ALT. 19/941 (2%) duloxetine treated patients versus 4/664 (0.6%) placebo patients developed values that were high.

Another way of examining this is via abnormal increases, even within the normal range. An abnormal change was defined as an increase >26U/L. 48/950 (5.1%) duloxetine treated patients versus 17/668 (2.5%) placebo treated patients met this threshold (Fishers Exact p=0.01).

It is difficult to ascribe clinical significance to these observations. There are no cases of jaundice, or hyperbilirubinemia associated with increases in hepatic analytes. It appears that duloxetine like many drugs may cause seemingly benign increases in LFTs that do not correlate with serious liver toxicity. One can not, however, rule out serious problems that might occur at a rate of less than 1/1000 at this point.

C-5.H Reporting of Seizures in Labeling

The PRECAUTIONS section of labeling includes a subsection on SEIZURES. This section sites [redacted] The SEIZURE subsection is inaccurate. Three of the four patients did not have what would usually be considered CNS seizure events.

The physicians Dr. Privitera for patient 028-3732 and Dr. Mattes for patients 124-3351 and 124-3362 were contacted during this review (fax transmission August 15, 2002 of sponsor's teleconference minutes with these two physicians). They stated that these patients had "leg twitches," "hypnic jerks or twitching" and that these events "should not be coded as a seizure."

The [ ] patients in the primary MDD database identified with seizures in the drafting labeling are described below.

Study	Patient	MedRA Preferred Term
F1J-MC-HMATb	028-3755	convulsion
F1J-MC-HMATb	028-3732	myoclonic seizure
F1J-MC-HMATb	124-3351	myoclonic seizure
F1J-MC-HMATb	124-3362	myoclonic seizure

Only patient HMATb 028-3755 lost consciousness. Patients HMATb 028-3732, HMATb 124-3351, and HMATb 124-3362 did not lose consciousness nor was the event considered a generalized tonic clonic, partial complex, or absence seizure. Patients HMATb 124-3351 and HMATb 124-3362 experienced events classified by the investigator as myoclonic jerk or twitching. Patient HMATb 028-3732 experienced an event classified by the investigator as myoclonic leg jerks. Through MedRA, these events were classified to the preferred term "myoclonic seizure." More detailed patient summaries are presented below.

F1J-MC-HMATb 028-3755 (summarized in the ISS, Table ISS.2.2.7.)
A 20-year-old female fell from a horse and experienced the serious adverse event of concussion on [ ] 11 days after being randomized to study drug, duloxetine 40 mg BID. Patient had a brief loss of consciousness and seizure after the fall. Serious adverse events noted on the case report form were accidental injury, acute brain syndrome (concussion), and convulsion. Patient was hospitalized for observation, with complaints of headache, dizziness, and lower back pain. Diagnostic evaluation included unspecified x-rays and a CT scan of the head. All tests were negative, the patient had no further seizure activity, and was discharged from the hospital on [ ] Patient completed the study. This patient is described in section VII.C-3 of this review and I concluded that her seizure was unlikely related to duloxetine treatment.

F1J-MC-HMATb 028-3732

Patient 028 3732, a 41 year old Caucasian male, experienced the adverse event of myoclonic seizure (preferred MedRA term is myoclonic seizure; the lower level term is myoclonic leg jerks) during the trial. On 28 Jun 2000, the patient was randomized to duloxetine 20 mg BID. On [ ] days after randomization to study drug the patient experienced leg twitches. The severity of the leg twitches was considered moderate. The patient experienced this adverse event until [ ] This adverse event was not considered serious at any time. Concomitant medications include atorvastatin, aspirin, and ibuprofen. On [ ] (baseline) the QT

interval was 410 ms and decreased to 369 ms on [redacted] (Visit 7). Laboratory analytes were within normal range throughout the trial. The patient completed the study.

F1J-MC-HMATb 124-3351

Patient 124-3351, a 40 year old African American male, experienced the adverse event of myoclonic seizure (preferred MedRA term is myoclonic seizure; lower level term is myoclonic jerks) during the trial. On 2 Aug 2000, the patient was randomized to duloxetine 20 mg BID. On [redacted] days after randomization to study drug, the patient experienced hypnic jerk or twitching. The severity of the hypnic jerk or twitch was considered mild. The patient experienced the adverse event until [redacted] It was not considered serious at any time. Concomitant medications included Rolaids, Pepcid, Tums, Mylanta, and Actifed. On [redacted] (baseline), the QT interval was 399 ms and on [redacted] the QT interval was 387 ms (Visit 7). Laboratory analytes were within normal range, except for mildly elevated ALT at baseline and at Visit 8 (27 Sep 2000).

F1J-MC-HMATb 124-3362

Patient 124 3362, a 55 year old Caucasian female, experienced the adverse event of myoclonic seizure (preferred MedRA term is myoclonic seizure; lower level term is myoclonic jerks) during the trial. On 16 Aug 2000, the patient was randomized to duloxetine 40 mg BID. On [redacted] days after randomization to study drug, the patient experienced hypnic jerk or twitching. The severity of the hypnic jerk or twitching was considered mild. The patient experienced this adverse event until [redacted] It was not considered serious at any time. Concomitant medications included Prempro, primotren, Sudafed, and diphenhydramine. On [redacted] (baseline) the QT interval was 415 ms and decreased to 396 ms on [redacted] (Visit 7). Laboratory analytes were within normal range, except for elevated cholesterol. The patient completed the study.

One patient in the secondary safety database experienced a seizure. Patient 901-7015 (duloxetine 20-mg/day) discontinued due to the serious adverse event of a seizure 22 days after randomization, and was hospitalized. The patient had been drinking far more alcohol than initially reported and then suddenly reduced intake a few days before the seizure. Patient was lost to follow up. It is unlikely that this event was drug related.

These cases do not represent a signal for increased seizure risk with duloxetine.

C-6 Common Adverse Events

Treatment emergent adverse events were categorized from their verbatim terms by the sponsor using the MedDRA dictionary. Translations for adverse events pertaining to sexual dysfunction and urinary retention, could have been grouped in a more useful manner and segregated by sex (see section C-5).

Otherwise translation of verbatim terms to MedDRA terms appears to be appropriate for common adverse events.

C-6.A Common and Drug Related Adverse Events

Treatment emergent adverse events were examined in the primary safety database by comparing the occurrence rates in the pooled placebo controlled studies. Events that were reported by at least 5% of duloxetine treated patients and at a rate that was at least twice the placebo rate were considered common and drug related adverse events.

Common and Drug Related Adverse Events in the Primary Placebo Controlled Pooled Database (occurrence rate of ≥5% and at least twice placebo)				
Adverse Events	**Placebo**		**Duloxetine**	
	(N=723)		**(N=1032)**	
	n	**(%)**	**n**	**(%)**
Nausea	50	(6.9)	225	(21.8)
Dry mouth	47	(6.5)	166	(16.1)
Fatigue	33	(4.6)	114	(11.0)
Dizziness (excluding vertigo)	38	(5.3)	110	(10.7)
Constipation	27	(3.7)	109	(10.6)
Somnolence	21	(2.9)	80	(7.8)
Appetite decreased NOS	15	(2.1)	67	(6.5)
Sweating increased	11	(1.5)	56	(5.4)

Nausea, dry mouth, fatigue, dizziness, and constipation are events that occurred in greater than 10-20% of patients taking duloxetine.

C-6.B Dose Dependency of Adverse Events

The sponsor did not identify any clear relationship between duloxetine dose and occurrence rates of spontaneously reported adverse events (Table C-6.B.2). This may be because flexible dose studies were pooled with fixed dose studies in the sponsor's analysis of this relationship. Studies HMAT (a) and (b) were the only studies where multiple fixed doses were employed. In study HMAT(b) Dizziness and dry mouth appeared to be dose dependent while the other common and drug related adverse events did not (Table C-6.B.1).

Table C-6.B.1 Common and drug related adverse events segregated by dose in study HMAT(b)

	Placebo	**Duloxetine 20-mg BID**	**Duloxetine 40-mg BID**	**Paroxetine 20-mg QD**	**Total**
	N=89	**N=86**	**N=91**	**N=87**	**N=353**
	n(%)	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Patients reporting at least 1 AE	61(68.5)	73(84.9)	76(83.5)	76(87.4)	286(81.0)
Nausea	2(2.2)	19(22.1)	23(25.3)	14(16.1)	58(16.4)
Insomnia	5(5.6)	15(17.4)	18(19.8)	7(8.0)	45(12.7)
Somnolence	2(2.2)	15(17.4)	10(11.0)	7(8.0)	34(9.6)
Dizziness	5(5.6)	**4(4.7)**	**15(16.5)**	9(10.3)	33(9.3)
Dry Mouth	3(3.4)	**9(10.5)**	**14(15.4)**	7(8.0)	33(9.3)
Constipation	3(3.4)	7(8.1)	8(8.8)	12(13.8)	30(8.5)
Sweating	0(0.0)	8(9.3)	11(12.1)	6(6.9)	25(7.1)

Spontaneously reported adverse events that occurred >5% of the time and at a rate twice that of placebo are enumerated in table C-6.B.2. The Division considers that adverse events that occur at twice the placebo rate and >5% of the time to be "common and drug related". As noted above, there is no clear dose relationship; however, this may be due to inappropriate pooling of grouped data.

Table C-6.B.2 Common and drug related adverse events segregated by dose in pooled placebo controlled studies in the primary safety database.

			Duloxetine							
	Placebo N=723		40-mg N=314		60-mg N=251		80-mg N=315		120-mg N=152	
	N	%	N	%	N	%	N	%	N	%
Nausea	50	(6.9)	41	(13.1)	95	(37.8)	63	(20.0)	26	(17.1)
Dry mouth	47	(6.5)	27	(8.6)	64	(25.5)	36	(11.4)	39	(25.7)
Dizziness (exc vertigo)	38	(5.3)	21	(6.7)	44	(17.5)	33	(10.5)	12	(7.9)
Fatigue	33	(4.6)	27	(8.6)	28	(11.2)	33	(10.5)	26	(17.1)
Constipation	27	(3.7)	24	(7.6)	33	(13.1)	31	(9.8)	21	(13.8)
Somnolence	21	(2.9)	21	(6.7)	20	(8.0)	21	(6.7)	18	(11.8)
Appetite decreased NOS	15	(2.1)	13	(4.1)	29	(11.6)	18	(5.7)	7	(4.6)
Sweating increased	11	(1.5)	13	(4.1)	4	(1.6)	15	(4.8)	24	(15.8)

C-6.C Other Spontaneously Reported Adverse Events

A table of spontaneously reported adverse events that occurred at least 0.5% of the time and greater than placebo may be found in the appendix (table C-6.C.1).

C-7 Standard Analyses and Exploration of Laboratory Data

Hepatic Analytes are covered extensively in section C-5.G of this review. Only other laboratory analytes shall be discussed in this section.

C-7.1 Analyses Based on Central Tendency

Mean hemoglobin and hematocrit dropped in the placebo group but not the duloxetine group. Several other laboratory analytes differed in a statistically significant but clinically insignificant manner. Table C-7.A.1 in the appendix enumerates these values. There were no mean changes in laboratory values of concern that were not discussed in section C-5.

C-7.2 Analysis of Outliers

Tabulation and Fisher's Exact Test analysis of incidence of PCS lab values at anytime during the study was performed. CPK was the only lab analyte that occurred significantly more frequently ($p=0.10$) in the duloxetine treated patients versus placebo treated patients in the primary placebo controlled safety database. Visual inspection of the incidence rates was also performed. Other PCS values were either isolated cases (≤ 2) or roughly equal to placebo. Criteria for PCS laboratory analytes may be found in the appendix in Table C-7.2.

PCS high CPK was noted in 15/942 (1.6%) of duloxetine treated patients versus 4/656 (0.6%) placebo treated patients. Patients who showed increases in CPK values meeting PCS criteria

were identified and evaluated to clarify the possible clinical significance of these observations. Two additional cases were similarly evaluated: HMAQ 101-1136 had a value greater than the PCS limit after stopping study drug and HMAU 102-1214 had a one-time extreme elevation. The following is the sponsor's discussion of the highest CPK cases:

Of the 24 duloxetine-treated patients in the primary controlled and uncontrolled database, 21 had values >600 U/L, 14 had values >1000 U/L, and 4 had values >5000 U/L. These counts represent nonexclusive rankings; in other words, the 14 values over 1000 U/L also include the 4 individual cases over 5000 U/L. Of the 4 placebo-treated patients, two had values that exceeded 1000 U/L. The highest observed value in the placebo-treated patients was 3720 U/L (HMAT 028-3789). The following discusses the 4 highest CPK cases:

- HMAU 102-1214 This was the highest value observed in a duloxetine-treated patient with a single observation of 22,240 U/L. This patient was a 30-year-old Argentinean female who had a CPK elevation 36 days after initiating therapy with duloxetine 60 mg BID. The elevated CPK in this patient was accompanied by an elevation in both ALT (155 IU/L) and AST (528 IU/L). Eight days later, while still taking duloxetine, the CPK had returned to a normal value of 198 U/L, as had the AST and ALT. The patient was asymptomatic throughout and had no evidence of cardiac, renal or muscular disease. The patient experienced a second, less marked, isolated elevation in CPK of 2160 U/L with an accompanying more modest elevation in AST of 68 U/L approximately 4 months later (the patient remained on the same dose of duloxetine). Serological examination for hepatitis A, B, C, and E were negative. Though one can not rule out a causal relationship between duloxetine and the elevated CPK, the fact that duloxetine treatment continued and the CPK values waxed and waned argues against a connection.

- HMAQ 106-1612, reported the resumption of intensive weight training at the time of the CPK elevation.
- HMAU 131-5184 a 20-year-old male, experienced an isolated elevation in CPK of 9485 U/L one week after initiating duloxetine treatment at 40 mg BID. The patient's other laboratory tests at that time were remarkable for a modest elevation of AST of 135 U/L, with normal BUN and creatinine values. The CPK returned to baseline and the patient completed the study without further incident.
- HMBH 101-1116 a 26-year-old male, experienced an isolated CPK elevation of 6020 U/L approximately 36 days after initiating duloxetine treatment at 60 mg QD. At the time of the elevation, the patient also had an ALT of 111 U/L and an AST of 48 U/L, with normal BUN and creatinine. Two days prior to this CPK elevation, the patient had sustained injury in a motor vehicle accident. This patient discontinued from the study due to lack of efficacy.

In the uncontrolled safety database, mean changes to endpoint were not significant. In repeated measures analysis of CPK, the mean increases were not significant at any visit. These results suggested that any elevations may be transient and that results from the placebo-controlled trials may have reflected mean changes to a transiently high point. These were a large number of patients treated for at least 6 months at a modal dose of 60 mg BID, the highest anticipated dose.

C-8 Standard Analysis and Exploration of Vital Signs and Weight
Blood pressure and heart rate changes associated with duloxetine treatment are covered in sections C-5.B and C-5.C. This section shall review the potential associations of duloxetine treatment on weight and pulse.

There is an approximate 2 bpm supine pulse increase in duloxetine (n=997) over placebo (n=698) treated patients. Duloxetine patients had a mean increase of 1.49 bpm versus a 0.45-bpm decrease in placebo patients. Standing pulse difference was 3-bpm but only a fraction of patients had standing vitals signs performed. The mean increase in pulse for duloxetine treated patients was 2.76-bpm (n=149) and decrease of 0.45-bpm in placebo patients (n=138) There were no differences in the rates of potentially clinically significant changes in pulse in the primary controlled safety database. Only 1 of 963 duloxetine treated patients had a PCS increase in pulse versus 0/667 placebo patients. There were 3/956 duloxetine patients and 3/665 placebo treated patients with PCS decreases in pulse. Elevated pulse ($\geq$100 bpm and an increase of at least 10-bpm) was more common among duloxetine treated patients than placebo treated patients (12/985 versus 2/689; Fisher's Exact p=0.054). This is consistent with but less frequent than the changes in blood pressure observed in these patients.

There was a small but statistically significant mean weight loss in patients taking duloxetine in the short term placebo controlled trials. Placebo patients gained 0.25 Kg versus duloxetine patients losing 0.54 Kg ($p<0.001$). The rate of PCS weight loss or gain was higher on placebo patients (2 high and 2 low /698) versus duloxetine treated patients (2 low and 1 high /996). Comparative data on long-term effects of duloxetine treatment on weight are not available.

C-9 Clinical Experience with Overdose
There is very limited experience with overdose of duloxetine. The clinical experience with duloxetine overdose comes from cases that were identified from the clinical trials that comprise the primary safety database. Patients in studies who have taken doses larger than the highest dose of duloxetine being researched in the clinical development program (that is, 240 mg/day) were identified as an overdose. To date, there have been four such cases of overdose (Study HMAU, Patients 135-5620, 142-6303, 101-1103, and 101-1104). The minimum ingestion was approximately 300 mg, while the highest reported overdose was approximately 1400 mg. All patients survived their episode of overdose.

In drug-drug interaction studies, activated charcoal significantly decreased duloxetine plasma concentrations and t½ , indicating its potential use in the management of duloxetine overdose.

D. Adequacy of Safety Testing
The safety testing is adequate. The sponsor has exposed enough patients to surpass the ICH guidelines for the safety testing of new drugs. Appropriate clinical monitoring was done to account for what was learned about the drug from the preclinical toxicology data.

E. Summary of Critical Safety Findings and Limitations of Data
There are limitations to this or any data set. Since duloxetine is a new chemical entity and this data represents the entirety of the human experience, rare and serious events may yet occur that

can not be predicted. Rare serious events that might occur in less that 1/1100 patients can not be detected with an exposure of roughly 3400 patients.

Duloxetine is adequately safe to use in the treatment of major depressive disorder. As with almost any drug, there are some adverse events that will not be tolerable for some patients. The adverse event profile for duloxetine appears to be similar to that of other SNRI drugs with some exceptions.

There were no deaths that were likely related to duloxetine treatment. Two serious episodes of hypotension, requiring hospitalization, occurred in association with duloxetine treatment, but there appears to be no systematic trends toward hypotension-serious or otherwise.

Common adverse events that are related to duloxetine treatment include nausea, dry mouth, fatigue, dizziness, constipation, somnolence, and decreased appetite.

Like venlafaxine, duloxetine treatment is associated with increases in blood pressure in a dose dependent fashion. There does not appear to be any indication that duloxetine has an associated risk for acute malignant hypertension as do the MAOI drugs; however, patients taking duloxetine should probably have blood pressures checked during regular office visits. Based on the data, patients with borderline high blood pressure might likely experience worsening of hypertension when treated with duloxetine.

Patients taking duloxetine may experience difficulty with sexual dysfunction. Sexual dysfunction was monitored in a systematic fashion during drug development. Results from the Arizona Sexual Experience Questionnaire (ASEX) suggested that men's ability to reach orgasm was the greatest problem associated with duloxetine treatment.

Like most antidepressants, duloxetine is associated with adverse events related to discontinuation of treatment. Tapering treatment dose will probably decrease both the incidence and intensity of these events; however, there is no data to suggest one tapering schedule over another. During the development program, patients were discontinued abruptly from treatment and experienced, dizziness, nausea, headache, paraesthesia, insomnia, diarrhea, nightmares, and at times vomiting.

Duloxetine treatment may be associated with transient increases in liver function tests (ALT, AST) and CPK. This perturbation of laboratory analytes does not appear to be connected with any clinical consequences at this point. These elevations are not associated with either jaundice or hepatic necrosis. I do not suggest that there is any value in monitoring any laboratory values in a routine way during duloxetine treatment. It is likely that some patients may have increases in LFTs, but patients who were continued on duloxetine did not experience any sequelae associated with these duloxetine associated increased LFTs. Usual clinical judgement should prevail.

VIII. Dosing, Regimen, and Administration Issues

The sponsor proposes a starting dose of 60-mg per day in a single dose.

The effectiveness of duloxetine in the treatment of DSM-IV–defined major depressive disorder (measured by reduction in HAMD17 total score) has been established in three positive studies: HMATb, HMBHa, and HMBHb. Two of these studies employed a single fixed dose of 60-mg/day. HMATb employed 20-mg BID and 40-mg BID dosing that was effective. The minimum effective dose therefore appears to be 20-mg BID. The forced titration studies (HMAQ a and b) that allowed for doses up to 60-mg BID failed. There were not distinguishable differences in treatment response between the 20-mg and 40-mg BID groups. There is no data to suggest that doses above 40-mg BID will be of any added value though one can not say that they might not be beneficial to some patients.

Duloxetine may be taken with or without food. Somnolence was both common and drug related, though not dose dependent; therefore, evening dosing for single dose administration would be reasonable.

Patients tolerated starting with single doses of 60-mg daily generally well. Target doses higher than this were stared at 20-mg BID in the clinical trials. It is therefore reasonable to suggest starting at 20-mg BID or single doses of up to 60-mg/day. Doses were increased by 10-20-mg BID on a weekly basis in the forced titration study. Doses greater than 60-mg/day should be divided BID because of a lack of data on single dosing greater than this. Doses higher than 120-mg/day (60-mg BID) are not recommended.

Tapering duloxetine on discontinuation is recommended. During the development program, patients were discontinued abruptly from treatment and experienced, dizziness, nausea, headache, paraesthesia, insomnia, diarrhea, nightmares, and at times vomiting. Tapering will more than likely decrease both the severity and incidence of discontinuation associated adverse events; however, no particular tapering regimen was tested.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The sponsor adequately investigated the effects of gender on safety and efficacy. There were no between sex differences with regard to efficacy even when three positive studies were pooled. There were between sex differences observed in plasma pharmacokinetics; however, there are no dose adjustments because of the large overlap in PK parameters between sexes. Though several differences in various adverse events were statistically significant by Breslow-Day analysis, none were clinically significant. These statistical differences appear to be driven by inter-sex differences in the adverse event frequencies reported in the placebo group. Reports of adverse events between sexes in the duloxetine treated patients were roughly the same by visual inspection.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

There were not a sufficient number of specific racial minority groups enrolled to make a meaningful analysis of efficacy or safety based on racial sub-grouping. Protocols were open for enrollment to all people and did not have quotas for enrolling racial sub-groups. Though there was insufficient data to analyze safety and efficacy on racial lines, they made adequate attempts to enroll patients of all groups, and they analyzed the data that they had. There is no reason to believe that there should be any difference in safety, efficacy, or PK based on past experience with other antidepressants and the metabolic profile of duloxetine.

There were not adequate numbers of older and younger patients to evaluate the safety and efficacy of duloxetine in these age groups. There were no differences in treatment efficacy (HAM-D17 change from baseline) between older (>65 years n=34) and younger adults <65 years n=998) in the primary placebo controlled safety database. PK differences were evaluated in special studies and though statistically significant differences were observed, these differences are not clinically relevant. There were a few statistically significant differences in the frequencies of spontaneously reported adverse events; however, these appear to be driven by the reporting rate differences in the placebo group rather than observed differences between age groups in the duloxetine treated patients.

C. Evaluation of Pediatric Program

The sponsor has not conducted clinical studies with duloxetine in the pediatric population. The sponsor has committed to consider pediatric studies and the design thereof after the completion of the review of NDA 21-427.

D. Pregnancy, Breast Feeding, And Other Health Related Conditions

Pregnancy, Labor, Delivery and Nursing-The effect of duloxetine on pregnancy, labor and delivery in humans is unknown. I recommend that duloxetine be placed in pregnancy category C. Because duloxetine and its metabolites cross the placenta in rats and because of the possibility that duloxetine and its metabolites may have adverse effects on the newborn, duloxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

Duloxetine and its metabolites are excreted into the milk of lactating rats. Excretion of duloxetine and its metabolites into human milk is unknown, but nursing while on duloxetine is not recommended

Smoking Status—Duloxetine bioavailability appears to be about 34% lower in smokers than in nonsmokers. Dosage modifications are not necessary.

Renal Insufficiency—Duloxetine Cmax and AUC values were approximately 2-fold higher in patients with end stage renal disease (ESRD) receiving chronic intermittent hemodialysis, compared with subjects with normal renal function. In contrast, the elimination half-life was similar in both groups. Studies have not been conducted in patients with a moderate degree of

renal dysfunction. Population PK analyses suggest that mild renal dysfunction has no significant effect on duloxetine apparent clearance. A lower dose should be considered for patients with ESRD .

Hepatic Insufficiency—Six cirrhotic patients had a mean duloxetine apparent plasma clearance that was approximately 15% that of age- and gender-matched healthy subjects after receiving a 20 mg dose of duloxetine. The Cmax was similar in the cirrhotic patients, but the half-life was 34 hours longer. A lower starting dose should be considered for patients with clinically significant liver impairment .

X. Draft Labeling Review

Review comments are imbedded in a copy of the draft labeling that is forwarded to Dr. Laughren, the Psychopharmacology Team Leader. This section will summarize major points of the draft labeling which this reviewer recommends modifying.

- The description [ ] were deleted as they were not pertinent to the proposed NDA.

- Descriptions [ ] are included in the sponsor's proposed labeling. I recommend that they be deleted as they represent additional claims [ ]

- The description of depressed patients [ ] was deleted as these are not part of the recognized diagnostic criteria for Major Depressive Disorder and could be construed as representing additional claims beyond the treatment of Major Depressive Disorder.

- The PRECAUTIONS section of labeling includes a subsection on SEIZURES. This section sites [ ]. The SEIZURE subsection is inaccurate. Three of the four patients did not have what would usually be considered CNS seizure events (see section VII C-5.H). The total number of patients exposed to duloxetine included in the draft labeling is — because those patients enrolled in the SAAW trial (SUI patients) were excluded. Thus only MDD patients are reflected in the draft labeling. Since the safety tables reflect the primary integrated safety database that includes patients SUI patients, the ~ denominator (only MDD patients) should probably be changed to avoid confusion and keep labeling as consistent as possible.

- The numbers of patients exposed in clinical trials and numbers of duloxetine treated patients with ECG data in labeling were inconsistent with the numbers in the ISS.

- The description of [ ] data in labeling is of little value to clinicians and does not convey the dose dependent increases in blood pressure observed in clinical trials. Elevated blood pressure was defined as systolic BP ≥140 and an increase of ≥10-mmHg and diastolic ≥90 and an increase of ≥10-mmHg. Treatment-emergent, elevated blood pressures in the placebo controlled database follows:

The above table along with the recommendation that patients taking duloxetine have blood pressures monitored on a regular basis should appear in labeling

XI. Conclusions and Recommendations

A. Conclusions

Based on the review of NDA 21-427, the 120-day safety update, additional amendments to the NDA received from the sponsor, I conclude that duloxetine is reasonably safe and effective in the treatment of patients with Major Depressive Disorder.

B. Recommendations

I recommend that the Division take an approvable action for NDA 21-427. Revisions to the sponsors draft labeling are described in section XI (Labeling Review).

Paul J. Andreason, MD
Clinical Reviewer, HFD-120

Appendix

Tables of Studies supporting NDA 21-427

Primary Safety Database in NDA 21-427

Study/ No. of Sites/ Location	Study Title	Study Design	No. of Patients/ By Gender/ Mean Age/ Age Range	Treatment (mg/ day)
F1J-MC-HMAQa 8 sites US	Duloxetine Versus Placebo in the Treatment of Major Depression	Multicenter, parallel, double-blind, randomized placebo-controlled, forced titration; double-blind placebo lead-in and lead-out	N= 173 (F= 111; M= 62) Mean age= 41. 4 Age range= 18.7-65.0	Duloxetine 20-60 mg PO BID Fluoxetine 20 mg PO QD
F1J-MC-HMAQb 11 sites US	Duloxetine Versus Placebo in the Treatment of Major Depression	Multicenter, parallel, double-blind, randomized, placebo-controlled, forced titration; double-blind placebo lead-in and lead-out	N= 194 (F= 129; M= 65) Mean age= 40. 4 Age range= 18.9-64.4	Duloxetine 20-60 mg PO BID Fluoxetine 20 mg PO QD
F1J-MC-HMATa 22 sites US	Duloxetine Versus Placebo and Paroxetine in the Acute Treatment of Major Depression	Multicenter, parallel, double-blind, randomized, placebo- and active comparator-controlled, fixed dose; double-blind placebo lead-in and lead-out	N= 354 (F= 218; M= 136) Mean age= 43. 7 Age range= 18.0-82.2	Duloxetine 20 mg or 40 mg PO BID Paroxetine 20 mg PO QD
F1J-MC-HMATb 22 sites US	Duloxetine Versus Placebo and Paroxetine in the Acute Treatment of Major Depression	Multicenter, parallel, double-blind, randomized, placebo- and active comparator-controlled, fixed dose; double-blind placebo lead-in and lead-out	N= 353 (F= 217; M= 136) Mean age= 40. 5 Age range= 18.2-78.2	Duloxetine 20 mg or 40 mg PO BID Paroxetine 20 mg PO QD
F1J-MC-HMBHa 18 sites US	Duloxetine Once-Daily Dosing Versus Placebo in the Acute Treatment of Major Depression	Multicenter, parallel, double-blind, placebo-controlled, fixed dose; blinded placebo lead-out	N= 245 (F= 163; M= 82) Mean age= 42. 4 Age range= 18.6-77.7	Duloxetine 60 mg PO QD

Primary Safety Database in NDA 21-427

F1J-MC-HMBHb 23 sites US	Duloxetine Once-Daily Dosing Versus Placebo in the Acute Treatment of Major Depression	Multicenter, parallel, double-blind, placebo-controlled, fixed dose; blinded placebo lead-out	N= 267 (F= 184; M= 83) Mean age= 40. 9 Age range= 19.2- 82.9	Duloxetine 60 mg PO QD
F1J-MC-HMAU: 52 study sites US, Canada, Mexico, South America	Long-Term Open-Label Treatment with Duloxetine Hydrochloride for Evaluation of Safety in Major Depression	Open-label N= 1282 only firsy 8-weeks considered in primary safety database total study length 54 weeks (52 weeks on drug)	M andF Age at least 18 Patients with MDD	Duloxetine40 mg or60 mg BID
F1J-MC-SAAW: 48 study sites US	Duloxetine Versus Placebo in the Relief of Stress Incontinence	Double-blind, placebo-controlled, randomized, 4-arm 20 weeks (12 weeks on drug)	F= 553 Ages 18-65 Healthy volunteers diagnosed with stress incontinence	Duloxetine 20 mg/ day, 20 mg BID, 40 mg BID or placebo/ PO

Secondary Safety Database -Completed Studies in NDA 21-427

STUDY: Title	Phase/ Design	Number of Patients/ Gender/ Age	Study Population	Duration of Treatment	Test Product/ Dosage/ Regimen Route of Admin.	Adverse Events Leading to D/C	SAEs
F1J-MC-HMAG: Duloxetine/Placebo in Major Depressive Disorder	Phase 1b-2/ Double-blind, stratified, randomized, parallel	Total: 105 Sex: M=48; F=57	Major depression	10 weeks	Dulox 20 mg QD Placebo	Dulox 20: 5 Placebo: 3 Total: 8	Dulox 20: 1 Placebo: 2 Total: 3
F1J-MC-HMAH: Duloxetine 20/30 mg Versus Placebo in Major Depression	Phase 2/ Double-blind, placebo-controlled, randomized, parallel	Total: 177 Sex: M=75; F=102	Major depression	54 weeks	Dulox 20, 30 mg QD Placebo	Dulox 20: 10 Placebo: 6 N/A: 1 Total: 17	Dulox 20: 11 Placebo: 8 N/A: 1 Total: 20
F1J-MC-HMAI: A Double-Blind, Placebo- and Clomipramine-Controlled Study of Duloxetine in Patients with Major Depression	Phase 2/ Randomized, parallel, double-blind, placebo- and active comparator-controlled	Total: 648 Sex: M=212 F=436	Major depression	55 weeks	Dulox 5, 10, 20 mg QD Clomipramine 150 mg BID Placebo	Dulox 5: 11 Dulox 10: 7 Dulox 20: 11 Clomip: 28 Placebo: 8 Total: 65	Dulox 5: 8 Dulox 10: 14 Dulox 20: 13 Clomip: 4 Placebo: 9 N/A: 1 Total: 49
F1J-EW-E001: A Pilot Study in Major Depressive Disorder	Phase 2/ Single arm, open label	Total: 93 Sex: M=31; F=62	Major depression	6 weeks	Dulox 20 mg QD	Dulox 20: 4 N/A: 1 Total: 5	Dulox 20: 4 Total: 4

Secondary Safety Database -Completed Studies in NDA 21-427

STUDY: Title	Phase/ Design	Number of Patients/ Gender/ Age	Study Population	Duration of Treatment	Test Product/ Dosage/ Regimen Route of Admin.	Adverse Events Leading to D/C	SAEs
F1J-MC-SAAA: Duloxetine Versus Placebo in Patients with Urinary Incontinence: Assessment of Subjective and Objective Parameters	Phase 2/ Double-blind, randomized, placebo-controlled	Total: 92 Sex: M=1; F=91	Urinary Incontinence	3 weeks	Dulox 20 mg QD Placebo	Dulox 20: 1 Placebo: 1 Total: 2	Placebo: 2 Total: 2
F1J-MC-SAAB: Duloxetine for Urinary Incontinence: A Multiple- Dose Study for Efficacy and Safety	Phase 2/ Double-blind, placebo-controlled, stratified, randomized, parallel	Total: 288 Sex: M=0; F=288	Urinary Incontinence	6 weeks	Dulox 20, 30, 40 mg QD Placebo	Dulox 20: 6 Dulox 30: 4 Dulox 30/40: 7 Placebo: 2 N/A: 6 Total: 25	Placebo: 2 N/A: 1 Total: 3
F1J-MC-SAAH: A Study of Duloxetine Hydrochloride Versus Placebo in Patients with Urinary Urgency and Proven Detrusor Overactivity	Phase 2/ Double-blind, placebo-controlled, randomized, parallel	Total: 32 Sex: M=5; F=27	LUTD	1 week (12-week extension)	Dulox 30, 40 mg QD Placebo	Dulox: 2 Placebo: 3 N/A: 1 Total: 6	Dulox 30: 1 Dulox 40: 1 Placebo: 1 Total: 3
F1J-MC-SAAI: Duloxetine Hydrochloride Versus Placebo in Patients with Irritative Symptoms of Benign Prostatic Hyperplasia	Phase 2/ Double-blind, placebo-controlled, randomized, parallel	Total: 91 Sex: M=91; F=0	LUTD	8 weeks	Dulox 30, 40 mg QD Placebo	Placebo/ Dulox 30: 3 Dulox 30: 6 Dulox 30/30: 1 Placebo: 1 Total: 11	Dulox 30: 1 Placebo: 1 Total: 2
F1J-MC-SAAL: Duloxetine Hydrochloride Versus Placebo and Oxybutynin in Patients with Symptoms of Urinary Urgency and Frequency	Phase 2/ Double-blind, placebo- and comparator-controlled, randomized, crossover	Total: 68 Sex: M=0; F=68	LUTD	8 weeks (1-week washout period)	Dulox 30, 40 mg QD Oxybutinin 7.5, 10 mg QD Placebo	Dulox/Oxy: 2 Dulox/ Placebo: 3 Oxy/Dulox: 3 Total: 8	0
F1J-MC-SAAW: Duloxetine Versus Placebo in the Relief of Stress Incontinence	Phase 2/ Double-blind, parallel, placebo-controlled	Total: 276 Sex: M=0; F=276	Urinary Incontinence	12 weeks	Dulox 20/day BID Placebo[a]	Dulox 20: 14 Placebo: 8 Total: 22	Dulox 20: 2 Placebo: 1 Total: 3

Secondary Safety Database Continued –Ongoing Studies

STUDY: Title	Phase/ Design	Number of Patients/ Gender/ Age	Study Population	Duration of Treatment	Test Product/ Dosage/ Regimen Route of Admin.	SAEs

Secondary Safety Database Continued –Ongoing Studies

STUDY: Title	Phase/ Design	Number of Patients/ Gender/ Age	Study Population	Duration of Treatment	Test Product/ Dosage/ Regimen Route of Admin.	SAEs
F1J-MC-HMAW: A Dose Response Study of Duloxetine versus Placebo in Patients with Painful Diabetic Neuropathy	Phase 2/3 Double-blind, parallel, placebo-controlled	Target: 440 Ages: >18	Patients with Diabetes and Diabetic Neuropathy	Dulox 12 weeks; 52-week open-label extension	Dulox 60 mg BID, Dulox 60 mg QD, Dulox 20 mg QD, Placebo	0
F1J-MC-HMAY(a): Duloxetine Versus Placebo and Paroxetine in the Treatment of Major Depression	Phase 3/ Double-blind, parallel, placebo- and active comparator-controlled	Target: 356 Ages: >18	Major depression	Dulox and Paroxetine: 35 weeks Placebo: 37 weeks	Dulox 40 to 60 mg BID Paroxetine 20 mg QD Placebo	0
F1J-MC-HMAY(b): Duloxetine Versus Placebo and Paroxetine in the Treatment of Major Depression	Phase 3/ Double-blind, parallel, placebo- and active comparator-controlled	Target: 356 Ages: >18	Major depression	Dulox and Paroxetine: 35 weeks Placebo: 37 weeks	Dulox 40 to 60 mg BID Paroxetine 20 mg QD Placebo	2
F1J-MC-SBAT: Efficacy and Safety of Duloxetine Compared with Placebo in Subjects with Stress Urinary Incontinence	Phase 3/ Double-blind, stratified, randomized, parallel, placebo-controlled	Target: F: 440 Ages: >18	Stress Urinary Incontinence	Dulox: 12 weeks Placebo: 14 weeks	Dulox 40 mg BID	2
F1J-MC-SBAV: Efficacy and Safety of Duloxetine Compared with Placebo in Subjects with Stress Urinary Incontinence	Phase 3/ Double-blind, stratified, randomized, parallel, placebo-controlled	Target: F: 600 Ages: >18	Stress Urinary Incontinence	Dulox: 12 weeks Placebo: 14 weeks	Dulox 40 mg BID	8
F1J-MC-SBAX: Efficacy and Safety of Duloxetine Compared with Placebo in Subjects with Stress Urinary Incontinence	Phase 3/ Double-blind, stratified, randomized, parallel, placebo-controlled	Target: F: 440 Ages: >18	Stress Urinary Incontinence	Dulox: 12 weeks Placebo: 14 weeks	Dulox 40 mg BID	0

Secondary Safety Database Continued –Ongoing Studies

STUDY: Title	Phase/ Design	Number of Patients/ Gender/ Age	Study Population	Duration of Treatment	Test Product/ Dosage/ Regimen Route of Admin.	SAEs
F1J-MC-SBAU: Long-Term Monitoring of Safety in Subjects Treated with Duloxetine for Stress Urinary Incontinence	Phase 3/ Open-label	Target: F: 440 Ages: >18	Stress Urinary Incontinence (patients who completed SBAT)	Until Dulox is commercially available for the treatment of SUI or sponsor stops the study	Dulox 40 mg BID	1
F1J-MC-SBAW: Long Term Monitoring of Safety in Subjects Treated with Duloxetine for Stress Urinary Incontinence	Phase 3/ Open-label	Target: F: 600 Ages: >18	Stress Urinary Incontinence (patients who completed SBAV)	Until Dulox is commercially available for the treatment of SUI or sponsor stops the study	Dulox 40 mg BID	1
F1J-MC-SBAY: Long Term Monitoring of Safety in Subjects Treated with Duloxetine for Stress Urinary Incontinence	Phase 3/ Open-label	Target: F: 600 Ages: >18	Stress Urinary Incontinence	Until Dulox is commercially available for the treatment of SUI or sponsor stops the study	Dulox 20 to 40 mg BID	2
F1J-MC-SBAM: Efficacy and Safety of Duloxetine Compared with Placebo in Subjects Electing Surgery for Pure Genuine Stress Incontinence	Phase 2/ Double-blind, stratified, randomized, parallel, placebo-controlled	Target: F: 100 Ages: >18 and <75	Patients who had decided to proceed toward surgery for severe pure genuine stress incontinence	Active period: Up to 12 weeks Open-label period: Until Dulox is commercially available for the treatment of SUI or sponsor stops the study	Dulox 40 to 60 mg BID	0
F1J-MC-SBBL: Efficacy and Safety of Duloxetine Compared with Placebo in Subjects with Symptoms of Bladder Overactivity Due to Pure Detrusor Instability or Sensory Urgency	Phase 2/ Double-blind, stratified, randomized, parallel, placebo-controlled	Target: F: 300 Ages: >18	Patients with symptoms of bladder overactivity established on urodynamic studies to be due either to pure detrusor instability or sensory urgency	Dulox: 12 weeks Placebo: 14 weeks	Dulox 40 to 60 mg/day BID	0

Secondary Safety Database Continued-Summary of Japanese Clinical Studies

STUDY: Title	Phase/ Design	Number of Patients Gender/ Age	Study Population	Duration	Test Product/ Dosage Regimen Route of Admin.	SAEs
F1J-JE-102G: Late Phase II Clinical Study About Depression and Depressive States in Psychiatry	Phase 2/ Open-label	Target: 60 Ages 20-69	Depression or depressive states	6 weeks	Duloxetine 10, 20, or 30 mg PO QAM	Dulox 10 mg: 1
F1J-JE-221G: Early Phase II Clinical Study -Effects on Depression and Depressive Conditions	Phase 2/ Open-label	Target: 80 Ages 20-69	Depression or depressive states	4 weeks	Duloxetine Initial dose 5 mg/day maximum dose 20 mg PO QAM	0
F1J-JE-301G: Early Phase II Clinical Study in the Field of Urology - Clinical Trial of the Drug's Action on Urinary Incontinence Induced by Increased Abdominal Pressure	Phase 2/ Open-label	Target: F=20 Ages 20-79	Stress urinary incontinence	4 weeks	Duloxetine Phase 1: 10 mg/day: Phase 2: 5 or 20 mg/day PO QAM	0
F1J-JE-311G: Long-Term Dosing Study of the Drug's Action Against Depression and Depressive Conditions in Psychosomatic Medicine Patients	Phase 3/ Open-label	Target: 100 Ages 20-69	Depression or depressive states	26-52 weeks	Duloxetine Initial dose 5 or 10 mg/day, maximum dose of 30 mg/day PO QAM	Dulox 30 mg: 1
F1J-JE-312G: Phase III Clinical Trial of the Drug's Action Against Depression and Depressive Conditions in Elderly Patients in the Field of Psychotherapeutic Medicine	Phase 3/ Open-label	Target: 50 Ages >65	Depression or depressive states	4 weeks	Duloxetine Initial dose of 5 mg/day maximum dose of 20 mg/day PO QD	Dulox 5 mg: 1
F1J-JE-313G: Clinical Trial of the Drug's Action Against Depression and Depressive Conditions in Psychosomatic Medicine Patients (Double-Blind Intergroup Comparison Study Using Trazodone Hydrochloride as a Comparator)	Phase 3/ Double-blind, non-controlled and active comparator-controlled	Target:200 Ages 20-69	Depression or depressive states	4 weeks	Duloxetine Group 1: 5 mg/day Group 2: 15 mg/day PO TID Trazodone Group 1: 75 mg/day Group 2: 150 mg PO TID	Trazodone 1
F1J-JE-321G: Long-Term Dosing Study of the Drug's Action Against Depression and Depressive Conditions in Psychiatric Patients	Phase 3/ Open-label	Target: 300 Ages 20-69	Depression or depressive states	26-52 weeks	Duloxetine Initial dose of 10 mg/day maximum dose of 40 mg/day PO QAM	Dulox 10 mg: 5 20 mg: 7 30 mg: 7 40 mg: 3 Total: 22
F1J-JE-322G: Phase III Clinical Trial of the Drug's Action on Depression and Depressive Conditions in Elderly Psychiatric Patients	Phase 3/ Open-label	Target: 50 Ages >65	Depression or depressive states	6 weeks	Duloxetine Initial dose 10 mg/day maximum dose 30 mg/day PO QAM	Dulox 20 mg: 1

Secondary Safety Database Continued-Summary of Japanese Clinical Studies

STUDY: Title	Phase/ Design	Number of Patients Gender/ Age	Study Population	Duration	Test Product/ Dosage Regimen Route of Admin.	SAEs
F1J-JE-323G: LY248686 Phase III Clinical Trial of the Drug's Action on Depression and Depressive Conditions in Psychiatric Patients (Double-Blind Intergroup Comparative Study Using Mianserin Hydrochloride as a Control)	Phase 3/ Double-blind, placebo-controlled, comparative	Target: 200 Ages 20-69	Depression or depressive states	4 weeks	Duloxetine Formulation A at 15 mg QD; Formulation B at 30 mg QD Mianserin 30 mg QD	Dulox 30 mg: 1 Mainserin: 1 Total: 2
F1J-JE-324G: Clinical Trial of the Drug's Action Against Depression and Depressive Conditions in Elderly Psychiatric Patients (2)	Phase 3/ Open-label	Target: 30 Ages >65	Depression or depressive states	6 weeks	Duloxetine Initial dose 10 mg/day maximum 30 mg/day PO QAM	Dulox 20 mg: 2
F1J-JE-401G: Clinical Trial of the Drug's Action on Urinary Frequency, Urgency, and Incontinence Caused by Neurogenic and Unstable Bladder with Uninhibited Contractions	Phase 2/ Open-label	Target: 20 per group Ages 20-79	Stress urinary incontinence	4 weeks	Duloxetine Group 1: 10 mg/day Group 2: 5 or 20 mg/day QD	Dulox 10 mg: 2
F1J-JE-1008: Early Phase II Clinical Study About Depression and Depressive States in Psychiatry	Phase 2/ Open-label	Target: 80 Ages 20-69	Depression or depressive states	6 weeks	Duloxetine Initial dose 10 mg/day maximum dose 30 mg/day QD	Dulox 10 mg: 2 20 mg: 1 30 mg: 1 Total: 4
F1J-JE-1009: Late Phase II Clinical Study Regarding Depression and Depressive States in Psychiatry	Phase 2/ Double-blind, active-comparator	Target: 200 Ages 20-69	Depression or depressive states	6 weeks	Duloxetine Initial dose 10 mg/day maximum 30 mg/day Imipramine Initial dose 50 mg/day maximum dose 150 mg/day	Dulox 20 mg: 1 Imipra-mine: 6 Total: 7

A. Other Relevant Materials

Table C Investigators and Sites in Pivotal studies

F1J-MC-HMBH Study Group A

Site ID#:	Primary Investigator Site Address	Number of Patients Enrolled	Number of Patients Discontinued
100	Asnis, Greg, MD Montefiore Medical Center 111 E 210 St Klau Basement Bronx, NY 10467 USA	6	2
102	Beckett, Louise, MD IPS Research 1211 N Shartel Ave Ste 407 Oklahoma City, OK 73103 USA	15	5
103	Croft, Harry, MD Croft Group Research Center 8038 Wurzbach Physicians Plaza 1, #480 San Antonio, TX 78229 USA	12	3
104	Debus, John, MD Research Institute of Dallas 5477 Glen Lakes Dr Ste 102 Dallas, TX 75231 USA	11	3
105	Diner, Bradley, MD Arkansas Psychiatric Clinic #5 St Vincent's Circle, #301 Little Rock, AK 72205 USA	6	5
123	Duboff, Eugene, MD Summit Research Network (Colorado) 4704 Harlan St Ste 500 Denver, CO 80212 USA	20	9
139	Eisen, Steve, MD ICSL Clinical Studies 400 Market St Ste 425 Philadelphia, PA 19106 USA	14	7

Table C Investigators and Sites in Pivotal studies

F1J-MC-HMBH Study Group A

Site ID#:	Primary Investigator Site Address	Number of Patients Enrolled	Number of Patients Discontinued
113	Gilliam, John, MD International Clinical Research Assoc 7650 E Parham Rd, Medical Bldg 2 Ste 240 Richmond, VA 23294 USA	12	7
121	Hartford, James, MD Hartford Research, LTD 273 Regency Ridge Dayton, OH 45459 USA	19	9
127	Haines, Francis, MD Clinical Studies, Ltd 40 Hemingway Dr East Providence, RI 02915 USA	4	1
108	Heiser, Jon, MD Pharmacology Research Institute 3576 Arlington Ave, Ste 301 Riverside, CA 92506 USA	8	3
128	Hassman, Howard, DO Comprehensive Clinical Research 130 White Horse Pike Clementon, NJ 08021 USA	14	1
126	Londborg, Peter, MD Summit Research Network, Inc 901 Boren Ave, Ste 1800 Seattle, WA 98104 USA	27	8
129	Miller, Janice, MD Clinical Neuroscience Solutions, PA 5601 Corporate way, Bldg #2 Ste 210 West Palm Beach, FL 33407 USA	29	12

Table C Investigators and Sites in Pivotal studies

F1J-MC-HMBH Study Group A

Site ID#:	Primary Investigator Site Address	Number of Patients Enrolled	Number of Patients Discontinued
124	Nunez, Margarita, MD ICSL Clinical Studies 780 95th Ave North, Ste 102 St Petersburg, FL 33702 USA	11	2
111	Smith, Ward, MD Summit Research Network, Inc 1849 NW Kearney St, Ste 201 Portland, OR 97209 USA	13	3
137	Wagemaker, Herbert, MD Clinical Neuroscience Solutions 4130 Salisbury Rd, Ste 2600 Jacksonville, FL 32216 USA	18	5
109	Weisler, Richard, MD 900 Ridgefield Dr Ste 320 Raleigh, NC 27609 USA	6	0

	F1J-MC-HMBH Study Group B		
Site ID#:	**Primary Investigator Site Address**	**Number of Patients Enrolled**	**Number of Patients Discontinued**
101	Bailey, Charles, MD Clinical Neuroscience Solutions 77 W Underwood St, 3rd Floor Orlando, FL 32806 USA	24	11
131	Bari, Mohammed, MD Synergy Clinical Research 450 4th Ave, Ste 409 Chula Vista, CA 91910 USA	3	1
106	Casat, Charles, MD Carolina Healthcare System 1300 Scott Ave Charlotte, NC 28211 USA	12	4
132	Cheren, Stanley, MD Access Clinical Studies 67 Union St, Fair 4 Natick, MA 01760 USA Satellite: Access Clinical Studies 209 Harvard St, Ste 405 Brookline, MA 02446	7	3
133	Cherlin, Edward, MD Valley Clinical Research 230 South 8th St El Centro, CA 92243 USA	0	0
119	Ginsberg, Lawerence, MD Red Oaks Psychiatry 17115 Red Oaks Dr, Ste 109 Houston, TX 77090	17	5
114	Hellerstein, David, MD **Changed** St Lukes Hospital 910 Ninth Ave. New York, NY 10019	6	2
138	Ishaque, Saleem, MD	7	4

	F1J-MC-HMBH Study Group B		
Site ID#:	Primary Investigator Site Address	Number of Patients Enrolled	Number of Patients Discontinued
	Synergy Clinical Research 6699 Alvarado Rd #2302 San Diego, CA 92120 USA		
134	Landbloom, Ronald, MD Regions Hospital 640 Jackson St St Paul, MN 55101 USA	8	1
141	Lefton, Theodore, MD and Beighley, Paul, MD ICSL Clinical Studies 2295 West Eau Gallie Blvd Melbourne, FL 32935 USA	7	1
140	Logue, Harry, MD Birmingham Psychiatry Pharmaceutical Studies 1 Independence Way, Ste 900 Birmingham, AL 35209 USA	2	1
120	Margolin, David, MD 1515 E Alluvial Ave Fresno, CA 93720 USA	9	3
130	McEntee, William, MD ICSL Clinical Studies 5969 Cattleridge Blvd Sarasota, FL 34232 USA	0	0
107	Mitchell, David, MD Laureate Psychiatric Clinic 6655 South Yale Ave Tulsa, OK 74136 USA	1	1
122	Privitera, William, MD	51	36

	F1J-MC-HMBH Study Group B		
Site ID#:	**Primary Investigator Site Address**	**Number of Patients Enrolled**	**Number of Patients Discontinued**
	Futuresearch Clinical Trials 4200 Marathon Blvd Ste 200 Austin, TX 78756 USA		
135	Rapaport, Mark, MD UCSD Psychopharmacology Research 8950 Villa La Jolla Dr, Ste 2243 La Jolla, CA 92037 USA	2	1
		11	5
117	Rynn, Moira, MD Univ of Penn School of Medicine University Science Center 3535 Market St, 6th Floor Philadelphia, PA 19104 USA Satellite: Greentree Medical Building 600 North Route 73, Ste 7 Marlton, NJ 08053		
116	Schaerf, Frederick, MD ICSL Clinical Studies 12751 New Brittany Blvd, Ste 501 Ft Myers, FL 33907	8	3
118	Strauss, Abbey, MD ICSL Clinical Studies 8200 Jog Rd Ste 101 Boynton Beach, FL 33437	5	2
115	Tigel, Phillip, MD California Clinical Trials 8501 Wilshire Blvd Beverly Hills, CA 90211 USA	62	17
112	Weinstein, Richard, MD Diablo Clincal Research 2255 Ygnacio Valley Rd Walnut Creek, CA 94598	25	9

	F1J-MC-HMAT Study Group B		
Site ID#:	**Primary Investigator Site Address**	**Number of Patients Enrolled**	**Number of Patients Discontinued**
039	Asnis, Gregory, MD Anxiety and Depression Clinic 344 Main St Mt Kisco, NY 10849 USA	4	2
004	Calabrese, Joseph, MD University Hospital of Cleveland Mood Disorder Ste 200 11400 Euclid Cleveland, OH 44106 USA	0	0
006	Cherlin, Edward, MD Behavioral Medical Research 230 South 8th St El Centro, CA 92243 USA	19	6
040	Cohen, Selwyn, MD Clinical Research Consultants 15 Corporate Dr Trumbull, CT 06611 USA	4	3
009	Cummins, Howard, PhD Institute for Advanced Clinical Research 7900 High School Road Elkins, Park, PA 19027 USA	9	4
037	Cutler, Andrew, MD Coordinated Research of Florida, Inc. 807 West Morse Blvd Suite 101 Winter Park, FL 32789 USA	18	15
011	Dietrich, Anthony, MD Neuropsychiatric Associates 5 the Green Woodstock, VT 05091 USA	10	4
012	Fabre, Louis, MD Fabre Research Clinic	22	8

	5503 Crawford St Houston, TX 77004 USA		
013	Fanelli, Joseph, MD Midwest Center 18 West 100 22nd St Suite 126 Oakbrook Terrace, IL 60181 USA	27	13
014	Feifel, David, MD UCSD Medical Center Dept of Psychiatry 200 W Arbor Dr San Diego, CA 92103 USA	0	0
017	Greist, John, MD Rogers Memorial Hospital 34700 Valley Road Oconomowoc, WI 53066 USA	15	2
038	Grosz, Daniel, MD Psychopharmacology Research Institute 8435 Reseda Blvd Northridge, CA 91324 USA	9	1
018	Holland, Peter, MD Boca Raton Medical Research Suite 202. South Plaza 7284 W Palmetto Road Boca Raton, FL 33433 USA	14	6
019	Hudson, James, MD McLean Hospital 115 Mill St Belmont, MA 02478 USA	19	7
024	Mattes, Jeffrey, MD Psychopharmacology Research Princeton Professional Park #A-12 601 Ewing Street Princeton, NJ 08540 USA	11	3
124	Satellite Site: 619 Dalton St. Emmaus, PA 18049	14	7

	USA		
025	Miller, Janice, MD Psychiatric Institute of Florida Suite 201 1840 Forest Hills Blvd West Plam Beach, FL 33406 USA	30	14
027	Petty, Fred, MD VA Medical Center Dallas #116-A 4500 South Lancaster Rd Dallas, TX 75216 USA Satellite Site: VA North Texas Health Care System Fort Worth Outpatient Clinic 200 West Rosedale St. Fort Worth, TX 76104	9	4
028	Privitera, William, MD Futuresearch Clinical Trials Suite #7 706 W Martin Luther King Blvd Austin, TX 78701 USA	81	35
030	Rapaport, Mark Hyman, MD UCSD Psychopharmacology Research Suite 2243 8950 Villa La Jolla Dr La Jolla, CA 92037 USA	20	8
036	Weihs, Karen, MD Clinical Psychiatric Research Center GWU Rose Hall, Room 612B 2300 Eye Street Washington, DC 20037 USA	18	7

Study HMAT Inclusion Criteria

Patients were included in the study only if they met **all** of the following criteria:

[1] Male or female outpatients at least 18 years of age.
[2] Had to sign the informed consent document.
[3] Met criteria for major depression, as defined by DSM-IV.
[4] HAMD17 total score =15 at Visits 1 and 2.
[5] CGI-Severity score =4 at Visitsland 2.
[6] Educational level and degree of understanding such that the patient could communicate intelligibly with the investigator and study coordinator.
[7] Judged to be reliable and agree to keep all appointments for clinic visits, tests, and procedures required by the protocol.

HMAT Exclusion Criteria

Patients were excluded from the study for **any** of the following reasons:
[8] Investigators and their immediate families. Immediate family was defined as the investigator's current spouse, parent, natural or legally adopted child (including a stepchild living in the investigator's household), grandparent, or grandchild.
[9] Treatment within the last 30 days with a drug that had not received regulatory approval at the time of study entry.
[10] Persons who had previously completed or withdrawn from this study or any other study investigating duloxetine hydrochloride.
[11] Any current DSM-IV diagnosis other than major depressive disorder, or any previous diagnosis of bipolar disorder, psychosis, or schizoaffective disorder. Additionally, patients diagnosed with dysthymic disorder within the past 2 years were excluded.
[12] Any anxiety disorder as a primary diagnosis within the past year (including panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, generalized anxiety disorder, and social phobia, but excluding specific phobias).
[13] The presence of an Axis II disorder which, in the judgment of the investigator, would interfere with compliance with the study protocol.
[14] History of substance abuse or dependence within the past year (drug categories defined in the DSM-IV), excluding nicotine and caffeine.
[15] A positive urine drug screen for any illicit substances of abuse. **Note:** If the patient had a positive drug screen for an illicit substance at Visit 1, a retest was allowed prior to Visit 2 if, in the judgment of the investigator, there was an acceptable explanation for the positive result. If the retest was posit ive, the patient was excluded.
[16] Women who were pregnant or breast-feeding; women of childbearing potential who were not using a medically accepted means of contraception when engaging in sexual intercourse: for example, intrauterine device, oral contraceptive, implant, Depo-Proverα Contraceptive Injection (sterile medroxyprogesterone acetate suspension, Pharmacia & Upjohn), barrier devices, or barrier devices with spermicide.
[17] Lack of response of the current episode of depression to two or more adequate courses of antidepressant therapy at a clinically appropriate dose for a minimum of 4 weeks.
[18] History of a lack of response, at any time, to an adequate trial of paroxetine for the treatment of depression (defined as treatment with at least 20 mg/day for a minimum of 4 weeks).
[19] Patients judged to be at serious suicidal risk.
[20] Serious medical illness, including any cardiovascular, hepatic, renal, respiratory, hematologic, endocrinologic, or neurologic disease, or clinically significant laboratory

abnormality. Clinically significant laboratory abnormalities were those that, in the judgment of the investigator, indicated a serious medical problem that would preclude study participation.
[21] Electroconvulsive therapy (ECT) within the past year.
[22] Initiating or stopping psychotherapy within 6 weeks prior to enrollment or initiating psychotherapy at any time during the study. Patients who initiated psychotherapy more than 6 weeks before enrollment could continue in therapy if, in the clinician's judgment, the therapy was not in its active phase. This judgment may have been made by inquiring whether there had been a change in the frequency of visits at the time of study enrollment, a stressful event, or change in the patient's symptomatology.
[23] Taking any excluded medications within 7 days prior to Visit 1. These medications were excluded because of their possible neurological effects that could interfere with the HAMD17 (primary efficacy measure), due to safety reasons, or due to the theoretical potential of these medications to mask adverse events.
[24] Treatment with a monoamine oxidase inhibitor within 14 days prior to Visit 1 or potential need to use a monoamine oxidase inhibitor within 2 weeks of discontinuation of study treatment.
[25] Treatment with fluoxetine within 30 dayspriortoVisit1.
[26] Frequent and/or severe allergic reactions with multiple medications, or known allergic reactions to any of the study drugs.
[27] Abnormal thyroid-stimulating hormone (TSH) concentrations. **Note:** Patients previously diagnosed with hyperthyroidism or hypothyroidism who had been treated with a stable dose of thyroid supplement for at least the past 6 months, had normal TSH concentrations, and were euthyroid were allowed into the study.
[28] Documented hypersensitivity or other contraindication to paroxetine use as defined in the prescribing information.

C-1.E Schedule of Events for HMAT(b)

Description of Data	V1	V2	V3	V4	V5	V6	V7	V8	V9	Early D/C
Weeks Until Next Visit:	1	1	1	1	2	2	2	2	N/A	
Informed consent	x									
Demographics	x									
Medical history/ Psychiatric history	x									
Height	x									
Weight, blood pressure, and heart rate	x	x	x	x	x	x	x	x	x	x
Physical examination	x									
Historical illness and previous medications	x									
Severity of Psychosocial Stressors	x									
MINI	x									
Preexisting conditions and adverse events	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x
Study drug dispensed		x	x	x	x	x	x	x		
Drug accountability			x	x	x	x	x	x	x	x
Patient summary including comments									x	x
ECG	x						x			x*
Laboratory Tests										
Hematology	x							x	x	x
Clinical chemistry and electrolyte group	x					x		x	x	x
Urine drug screen	x									
Urinalysis	x							x		
Pregnancy test (all females)	x									
Thyroid function test (TSH)	x									
Efficacy/Health Outcome Measures										
CGI-Severity	x	x	x	x	x	x	x	x	x	x
$^{HAMD}17$	x	x	x	x	x	x	x	x	x	x
MADRS		x	x	x	x	x	x	x	x	x
HAMA		x	x	x	x	x	x	x	x	x
PGI-Improvement			x	x	x	x	x	x	x	x
ASEX		x					x	x	x	x*
VAS		x	x	x	x	x	x	x	x	x
SSI		x	x	x	x	x	x	x	x	x
Health Resource Utilization Measure		x			x	x	x	x	x	x
Quality of Life in Depression Scale		x					x	x	x	x*

x = Performed at this visit. * = Administered only if patient discontinued before Visit 7.

Abbreviations: Early D/C = early discontinuation; CGI-Severity = Clinical Global Impressions of Severity; HAMD 17 = 17-Item Hamilton Depression Rating Scale; MADRS = Montgomery and Asberg Depression Rating Scale; HAMA = Hamilton Anxiety Rating Scale; PGI-Improvement = Patient's Global Impressions of Improvement; ASEX = Arizona Sexual Experiences Scale; VAS = Visual Analog Scales; SSI = Somatic Symptom Inventory.

Table C-1.G.1 Patient demographic Characteristics for Study HMAT(b)

Variable	PLACEBO (N=89)	DLX 20 BID (N=86)	DLX 40 BID (N=91)	PRX 20 QD (N=87)	Total (N=353)	p-Value
AGE: YRS						
No. Patients	89	86	91	87	353	.949**
Mean	40.14	40.69	40.89	40.25	40.50	
Median	41.28	40.05	40.83	39.25	40.29	
Standard Dev.	12.94	10.04	11.90	11.02	11.50	
Minimum	20.07	20.56	18.20	19.18	18.20	
Maximum	78.21	70.60	68.87	64.02	78.21	
HEIGHT: CM (Visit: 1)						
No. Patients	89	85	91	87	352	.556**
Mean	170.84	170.66	169.45	169.19	170.03	
Median	170.18	167.64	167.64	170.18	167.64	
Standard Dev.	9.69	9.66	10.72	9.79	9.97	
Minimum	152.40	152.40	139.70	149.86	139.70	
Maximum	198.12	200.66	195.58	193.04	200.66	
Unspecified	0	1	0	0	1	
WEIGHT: KG (Visit: 1)						
No. Patients	88	86	90	87	351	.071**
Mean	80.22	81.61	82.19	88.75	83.18	
Median	77.86	78.09	81.95	79.00	79.00	
Standard Dev.	18.93	20.33	20.87	28.97	22.74	
Minimum	45.40	51.76	43.58	45.40	43.58	
Maximum	153.91	165.26	155.72	194.31	194.31	
Unspecified	1	0	1	0	2	
ORIGIN: NO. (%)						
No. Patients	89	86	91	87	353	.270*
African Descent	8 (9.0)	4 (4.7)	5 (5.5)	9 (10.3)	26 (7.4)	
Western Asian	0	0	0	2 (2.3)	2 (0.6)	
Caucasian	74 (83.1)	72 (83.7)	77 (84.6)	64 (73.6)	287 (81.3)	
East/Southeast A	1 (1.1)	0	0	0	1 (0.3)	
Hispanic	6 (6.7)	9 (10.5)	9 (9.9)	12 (13.8)	36 (10.2)	
Other	0	1 (1.2)	0	0	1 (0.3)	
GENDER: NO. (%)						
No. Patients	89	86	91	87	353	.633*
Female	57 (64.0)	48 (55.8)	56 (61.5)	56 (64.4)	217 (61.5)	
Male	32 (36.0)	38 (44.2)	35 (38.5)	31 (35.6)	136 (38.5)	
HAMD Total (Visit: 3)						
No. Patients	89	86	91	87	353	.298**
Mean	17.20	18.74	17.86	17.83	17.90	
Median	17.00	18.50	18.00	17.00	18.00	
Standard Dev.	5.08	5.97	4.66	5.19	5.25	
Minimum	4.00	5.00	8.00	3.00	3.00	
Maximum	30.00	32.00	31.00	29.00	32.00	
CGI-SEVERITY (Visit: 3)						
No. Patients	89	86	91	87	353	.614**

Table C-1.G.1 Patient demographic Characteristics for Study HMAT(b)

	PLACEBO	DLX 20 BID	DLX 40 BID	PRX 20 QD	Total	p-Value
Mean	4.11	4.19	4.09	4.06	4.11	
Median	4.00	4.00	4.00	4.00	4.00	
Standard Dev.	0.73	0.79	0.51	0.65	0.68	
Minimum	2.00	1.00	3.00	2.00	1.00	
Maximum	6.00	6.00	5.00	6.00	6.00	
MADRS TOTAL (Visit: 3)						
No. Patients	89	86	91	87	353	.212**
Mean	22.72	24.48	22.23	23.29	23.16	
Median	22.00	25.50	23.00	23.00	23.00	
Standard Dev.	7.96	8.20	6.48	7.72	7.62	
Minimum	3.00	3.00	5.00	6.00	3.00	
Maximum	42.00	39.00	40.00	44.00	44.00	

* Frequencies are analyzed using a Chi- Square test.

** Means are analyzed using a Type III Sum of Squares analysis of variance

Table C-3.E HMBH a and b Schedule of Events

Description of Data	V1	V2	V3	V4	V5	V6	V7	V8	V9	Early D/C
Weeks Until Next Visit:	1	1	1	1	2	2	2	2	N/A	
Informed consent	x									
Demographics	x									
Medical history/Psychiatric history	x									
Height	x									
Weight, blood pressure, and heart rate	x	x	x	x	x	x	x	x	x	x
Physical examination	x									
Historical illness and previous medications	x									
Severity of Psychosocial Stressors								x	x	x
MINI	x									
Preexisting conditions and adverse events	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x
Study drug dispensed		x	x	x	x	x	x	x		
Drug accountability			x	x	x	x	x	x	x	x
Patient summary including comments									x	x
ECG	x									
Laboratory Tests										
Hematology	x					x		x	x	x
Clinical chemistry and electrolyte group	x					x		x	x	x
Urine drug screen	x									
Urinalysis	x									
Pregnancy test (all females)	x									
Thyroid function test (TSH)	x									
Efficacy/Health Outcome Measures										
CGI-Severity	x	x	x	x	x	x	x	x	x	x
$HAMD_{17}$	x	x	x	x	x	x	x	x	x	x
PGI-Improvement			x	x	x	x	x	x	x	x
VAS		x	x	x	x	x	x	x	x	x
SSI		x	x	x	x	x	x	x	x	x
QLDS		x						x	x	x

x = Performed at this visit.

Abbreviations: CGI-Severity = Clinical Global Impression of Severity; early D/C = early discontinuation; ECG = electrocardiogram; $HAMD_{17}$ = 17-Item Hamilton Depression Rating Scale; MINI = Mini International Neuropsychiatric Interview; PGI-Improvement = Patient Global Impression of Improvement; VAS = Visual Analog Scales; SSI = Somatic Symptom Inventory; QLDS = Quality of Life Depression Scale.

Table C-3.G Demographic Characteristics in study HMBHa

Variable	Placebo (N=122)	DLX 60 QD (N=123)	Total (N=245)	p-Value
ORIGIN: NO. (%)				
African Descent	6 (4.9)	3 (2.4)	9 (3.7)	.145*
Caucasian	103 (84.4)	107 (87.0)	210 (85.7)	
East/Southeast A	1 (0.8)	0	1 (0.4)	
Hispanic	12 (9.8)	9 (7.3)	21 (8.6)	
Other	0	4 (3.3)	4 (1.6)	
GENDER: NO. (%)				
Female	83 (68.0)	80 (65.0)	163 (66.5)	.685*
Male	39 (32.0)	43 (35.0)	82 (33.5)	
AGE: YRS				
Mean	42.34	42.44	42.39	.936**
Median	40.93	43.27	41.74	
Standard Dev.	12.58	13.74	13.15	
Minimum	18.59	18.66	18.59	
Maximum	77.68	75.54	77.68	

Table C-5.E schedule of assessments in protocol HMAQ

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**Early D/C**
Activity														
Informed Consent	x													
Medical History	x													
Height	x													
Weight	x	x	x	x	x	x	x	x	x	x	x	x	x	
Supine and Standing Heart Rate and Blood Pressure	x	x	x	x	x	x	x	x	x	x	x	x	x	
Physical Examination	x												x	x
Electrocardiogram	x													
Demographics	x													
Consumptive Habits	x													
Severity of Psychosocial Stressors	x													
Preexisting Conditions	x													
Historical Diagnoses	x													
Psychiatric History	x													
Family Psychiatric History	x													
Previous Psychiatric Drug Therapy	x													
Concomitant Medications	x	x	x	x	x	x	x	x	x	x	x	x	x	
Diagnosis of DSM-IV Major Depressive Disorder: MINI	x													

Table C-5.E schedule of assessments in protocol HMAQ

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	Early D/C
Clinician-rated HAMD17	x	x	x	x	x	x	x	x	x	x	x	x	x	
MADRS	x	x	x	x	x	x	x	x	x	x	x	x	x	
HAMA	x	x	x	x	x	x	x	x	x	x	x	x	x	
CGI-Severity	x	x	x	x	x	x	x	x	x	x	x	x	x	
CGI-Improvement		x	x	x	x	x	x	x	x	x	x	x	x	
PGI-Improvement			x	x	x	x	x	x	x	x	x	x	x	
IVR Patient-rated HAMD17	x	x	x	x	x	x	x	x	x	x	x	x	x	
SF-36	x					x						x		
Spontaneous Adverse Events		x	x	x	x	x	x	x	x	x	x	x	x	
Arizona Sexual Experiences Scale	x					x						x		
Hematology	x											x		x
Chemistry	x					x				x		x		x
Urinalysis	x											x		x
Urine Drug Screen	x													
Pregnancy Test (if applicable)	x													
Thyroid Stimulating Hormone	x													
Duloxetine Plasma Level				x		x		x		x		x		x
Study Drug Dispensed		x	x	x	x	x	x	x	x	x	x			
Drug Accountability			x	x	x	x	x	x	x	x	x	x		
Patient Treatment Speculation													x	x
Clinician Treatment Speculation													x	x
Patient Summary													x	x

Table C-5.H.1 HMAQ(a) Mean Change from Baseline (LOCF) HAM-D17 Total Score

	Baseline						Endpoint						Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	p-value
Placebo	57	20.56	3.81	21.0			13.95	7.29	14.0			-6.61	6.21	-7.0			
Dulox	56	19.64	3.30	19.5			11.38	7.88	10.0			-8.27	7.50	-8.0			0.15
Fluox	27	19.19	3.41	18.0			12.59	8.00	12.0			-6.59	8.23	-9.0			0.75

Table C-5.H.2 HMAQ(b) Mean Change from Baseline (LOCF) HAM-D17 Total Score

	Baseline						Endpoint					Change					
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	p-value
Placebo	55	20.42	4.12	20.0			13.65	7.06	14.0			-6.76	6.66	-5.0			
Dulox	61	19.90	4.20	19.0			13.10	8.68	11.0			-6.80	7.20	-8.0			0.96
Fluox	30	21.43	3.64	21.0			14.40	7.50	15.5			-7.03	7.19	-6.5			0.85

p-values represent comparisons of active treatment versus placebo

Table VII.C-3.1 Serious Adverse Events in Controlled Trials of the Primary Database

STUDY Patient Number	Treatment Group	Event(s) MedDRA Preferred Term
F1J-MC-HMAQb		
118-2818	Placebo	Gastrointestinal infection NOS
119-2915	Placebo	Food Poisoning NOS Abdominal Pain NOS
F1J-MC-HMATa		
035-4418	Duloxetine 40 mg BID (event occurred 4 days after patient stopped study drug)	Cardio-respiratory arrest Death
021-3008	Placebo	Asthma NOS
F1J-MC-HMATb		
028-3755	Duloxetine 40 mg BID	Fall, Concussion, Convulsion NOS
F1J-MC-HMBHa		
124-3403	Placebo (Event occurred 4 days after patient started in placebo lead out.)	Pneumonia NOS, Emphysema
F1J-MC-HMBHa		
129-3914	Placebo	Chest pressure sensation
121-3118	Placebo	Umbilical hernia NOS
F1J-MC-HMBHb		
122-3223	Duloxetine 60 mg QD	Calculus renal NOS
134-4410	Duloxetine 60 mg QD	Breast cancer female NOS
F1J-MC-SAAW		
026-1266	Duloxetine 40 mg BID	Dermatitis NOS, Asthma NOS, Urinary tract infection NOS
034-1668	Duloxetine 40 mg BID	Breast cancer NOS
040-1993	Duloxetine 20 mg BID	Spinal fusion surgery
043-2115	Duloxetine 20 mg BID	Appendicitis
006-0252	Placebo	Breast cancer recurrent

Table VII.C-3.2 Serious Adverse Events in Study HMAU (Uncontrolled Primary Safety Database)

	Duloxetine (N=1279)	
Preferred Term	**n**	**(%)**
Patients with one or more SAE	64	(5.0)
Patients with no SAE	1215	(95.0)
Suicidal ideation	7	(0.5)
Suicide attempt	7	(0.5)
Accident NOS	3	(0.2)
Hip fracture	3	(0.2)
Angina pectoris	2	(0.2)
Anxiety NEC	2	(0.2)
Cholelithiasis	2	(0.2)
Confusion	2	(0.2)
Depression aggravated	2	(0.2)
Depression NOS	2	(0.2)
Mania	2	(0.2)
Non-accidental overdose	2	(0.2)
Abdominal pain NOS	1	(0.1)
Abnormal behaviour NOS	1	(0.1)
Acute myocardial infarction	1	(0.1)
Acute stress disorder	1	(0.1)
Agitation	1	(0.1)
Alcohol poisoning	1	(0.1)
Anger	1	(0.1)
Basal cell carcinoma	1	(0.1)
Cardiac arrest	1	(0.1)
Cerebrovascular disorder NOS	1	(0.1)
Cervical operation NOS	1	(0.1)
Chest pain	1	(0.1)
Chronic obstructive airways disease	1	(0.1)
Colectomy NOS	1	(0.1)
Colon cancer NOS	1	(0.1)
Complication of pregnancy NOS	1	(0.1)
Conversion disorder	1	(0.1)
Coronary artery atherosclerosis	1	(0.1)
Dementia NOS	1	(0.1)
Dizziness (excl vertigo)	1	(0.1)
Electrocardiogram abnormal NOS	1	(0.1)
Endometrial hyperplasia	1	(0.1)
Fractured pelvis NOS	1	(0.1)
Gastritis NOS	1	(0.1)
Hypersensitivity NOS	1	(0.1)
Hypertension NOS	1	(0.1)

Hypomania	1	(0.1)
Insomnia	1	(0.1)
Intra-abdominal haemorrhage NOS	1	(0.1)
Lower limb fracture NOS	1	(0.1)
Lung squamous cell carcinoma stage unspecified	1	(0.1)
Malignant melanoma of skin stage unspecified	1	(0.1)
Myocardial infarction	1	(0.1)
Myocardial ischaemia	1	(0.1)
Oophorectomy NOS	1	(0.1)
Ovarian cyst	1	(0.1)
Palpitations	1	(0.1)
Pyelonephritis NOS	1	(0.1)
Salpingectomy	1	(0.1)
Syncope	1	(0.1)
Systemic lupus erythematosus	1	(0.1)
Thrombocytopenia	1	(0.1)
Upper limb fracture NOS	1	(0.1)
Uterine fibroids	1	(0.1)
Vaginal haemorrhage	1	(0.1)

Table C-5.C.4 Criteria for Declaring Vital Sign Values Potentially Clinically Significant

Parameter	Low	High
Supine systolic BP (mm Hg)	≤90 + dec. ≥20	≥180 + inc. ≥20
Standing systolic BP (mm Hg)	≤90 + dec. ≥20	≥180 + inc. ≥20
Supine diastolic BP (mm Hg)	≤50 + dec. ≥15	≥105 + inc. ≥15
Standing diastolic BP (mm Hg)	≤50 + dec. ≥15	≥105 + inc. ≥15
Supine pulse (bpm)	≤50 + dec. ≥15	≥120 + inc. ≥15
Standing pulse (bpm)	≤50 + dec. ≥15	≥120 + inc. ≥15

Rates of Occurrence of PCS Changes in Vital Signs in the Placebo Controlled Primary Safety Database

		Duloxetine			Placebo			Fisher's Exact
Vital Statistic	Abnormality	N	n	Percent	N	n	Percent	P-value
Supine Systolic BP	Low	987	9	0.9 %	690	11	1.6 %	.254
Supine Systolic BP	High	996	3	0.3 %	698	1	0.1 %	.647
Supine Diastolic BP	Low	993	7	0.7 %	690	2	0.3 %	.323
Supine Diastolic BP	High	996	5	0.5 %	697	1	0.1 %	.410
Supine Pulse	High	997	1	0.1 %	697	0	0.0 %	1.00
Standing Systolic BP	Low	143	3	2.1 %	138	2	1.4 %	1.00
Standing Systolic BP	High	149	0	0.0 %	138	0	0.0 %	
Standing Diastolic BP	Low	148	1	0.7 %	138	3	2.2 %	.356
Standing Diastolic BP	High	149	1	0.7 %	138	0	0.0 %	1.00

Table C-6.C.1 Treatment Emergent Adverse Events Occurring at Least 0.5% and ≥ to Placebo in the Primary Placebo Controlled Pooled Database. (Descending in Order of Occurrence in Duloxetine Treated Patients)

Adverse Events	Placebo (N=723)		Duloxetine (N=1032)		P-value Fishers Exact Test(2 Tail)	P-value for CMH General Association
	n	(%)	n	(%)		
Nausea	50	(6.9)	225	(21.8)	<.001	<.001
Headache NOS	125	(17.3)	179	(17.3)	1.00	.588
Dry mouth	47	(6.5)	166	(16.1)	<.001	<.001
Fatigue	33	(4.6)	114	(11.0)	<.001	<.001
Insomnia NEC	41	(5.7)	113	(10.9)	<.001	<.001
Dizziness (exc vertigo)	38	(5.3)	110	(10.7)	<.001	<.001
Constipation	27	(3.7)	109	(10.6)	<.001	<.001
Diarrhoea NOS	45	(6.2)	92	(8.9)	.046	.014
Somnolence	21	(2.9)	80	(7.8)	<.001	<.001
Appetite decreased NOS	15	(2.1)	67	(6.5)	<.001	<.001
Sweating increased	11	(1.5)	56	(5.4)	<.001	<.001
Vomiting NOS	20	(2.8)	49	(4.7)	.045	.013
Vision blurred	10	(1.4)	41	(4.0)	.001	<.001
Libido decreased	5	(0.7)	32	(3.1)	<.001	<.001
Anxiety NEC	16	(2.2)	31	(3.0)	.368	.205
Cough	21	(2.9)	30	(2.9)	1.00	.790
Hot flushes NOS	7	(1.0)	30	(2.9)	.006	.008
Anorgasmia	0	(0.0)	25	(2.4)	<.001	<.001
Yawning	0	(0.0)	25	(2.4)	<.001	<.001
Abdominal pain upper	12	(1.7)	24	(2.3)	.394	.370
Palpitations	13	(1.8)	24	(2.3)	.503	.304
Feeling jittery	3	(0.4)	22	(2.1)	.002	.003
Tremor NEC	5	(0.7)	22	(2.1)	.017	.010
Tinnitus	8	(1.1)	21	(2.0)	.182	.071
Loose stools	10	(1.4)	20	(1.9)	.456	.216
Urinary frequency	14	(1.9)	20	(1.9)	1.00	.796
Middle insomnia	3	(0.4)	19	(1.8)	.008	.006
Muscle spasms	4	(0.6)	18	(1.7)	.029	.014
Weight decreased	4	(0.6)	18	(1.7)	.029	.006
Anorexia	1	(0.1)	17	(1.6)	.001	.002
Sedation	6	(0.8)	17	(1.6)	.200	.082
Abnormal dreams	6	(0.8)	16	(1.6)	.199	.148
Lethargy	2	(0.3)	16	(1.6)	.008	.006
Chest pain NEC	5	(0.7)	15	(1.5)	.173	.085
Night sweats	2	(0.3)	15	(1.5)	.013	.007
Pyrexia	11	(1.5)	15	(1.5)	1.00	.979

Table C-6.C.1 Treatment Emergent Adverse Events Occurring at Least 0.5% and ≥ to Placebo in the Primary Placebo Controlled Pooled Database. (Descending in Order of Occurrence in Duloxetine Treated Patients)

Adverse Events	Placebo (N=723)		Duloxetine (N=1032)		P-value Fishers Exact Test(2 Tail)	P-value for CMH General Association
	n	(%)	n	(%)		
Upper respiratory tract infection viral NOS	10	(1.4)	15	(1.5)	1.00	.357
Ejaculation failure	2	(0.3)	14	(1.4)	.020	.024
Muscle twitching	4	(0.6)	14	(1.4)	.147	.054
Unexpected therapeutic effect	7	(1.0)	14	(1.4)	.512	.620
Blood pressure increased	3	(0.4)	12	(1.2)	.117	.096
Bronchitis NOS	6	(0.8)	12	(1.2)	.632	.808
Sleep disorder NOS	4	(0.6)	12	(1.2)	.212	.142
Thirst	2	(0.3)	12	(1.2)	.054	.039
Agitation	6	(0.8)	11	(1.1)	.805	.461
Bruxism	0	(0.0)	11	(1.1)	.004	.009
Erectile disturbance	2	(0.3)	11	(1.1)	.087	.035
Feeling abnormal	3	(0.4)	11	(1.1)	.175	.166
Initial insomnia	5	(0.7)	11	(1.1)	.458	.173
Pain NOS	6	(0.8)	11	(1.1)	.805	.399
Restlessness	3	(0.4)	11	(1.1)	.175	.059
Gastroenteritis viral NOS	5	(0.7)	10	(1.0)	.608	.528
Hypersomnia	2	(0.3)	10	(1.0)	.138	.045
Influenza like illness	5	(0.7)	10	(1.0)	.608	.659
Nervousness	4	(0.6)	10	(1.0)	.421	.239
Dyspnoea NOS	5	(0.7)	9	(0.9)	.789	.578
Pruritus NOS	5	(0.7)	9	(0.9)	.789	.680
Taste disturbance	3	(0.4)	9	(0.9)	.379	.238
Muscle cramps	5	(0.7)	8	(0.8)	1.00	.853
Pharyngitis NOS	5	(0.7)	8	(0.8)	1.00	.518
Dry skin	0	(0.0)	7	(0.7)	.046	.019
Ejaculation disorder NOS	1	(0.1)	7	(0.7)	.151	.085
Haemorrhoids	0	(0.0)	7	(0.7)	.046	.026
Orgasm abnormal	4	(0.6)	7	(0.7)	1.00	.557
Sexual dysfunction NOS	0	(0.0)	7	(0.7)	.046	.017
Throat irritation	1	(0.1)	7	(0.7)	.151	.111
Toothache	5	(0.7)	7	(0.7)	1.00	.985
Vaginosis fungal NOS	1	(0.1)	7	(0.7)	.151	.109
Weakness	5	(0.7)	7	(0.7)	1.00	.789
Blepharospasm	5	(0.7)	6	(0.6)	.768	.787
Central nervous system	2	(0.3)	6	(0.6)	.483	.279

Table C-6.C.1 Treatment Emergent Adverse Events Occurring at Least 0.5% and ≥ to Placebo in the Primary Placebo Controlled Pooled Database. (Descending in Order of Occurrence in Duloxetine Treated Patients)

Adverse Events	Placebo (N=723)		Duloxetine (N=1032)		P-value Fishers Exact Test(2 Tail)	P-value for CMH General Association
	n	(%)	n	(%)		
stimulation NOS						
Contusion	3	(0.4)	6	(0.6)	.744	.449
Dermatitis contact	0	(0.0)	6	(0.6)	.046	.025
Fall	2	(0.3)	6	(0.6)	.483	.380
Heart rate increased	3	(0.4)	6	(0.6)	.744	.485
Herpes simplex	3	(0.4)	6	(0.6)	.744	.431
Menstruation irregular	2	(0.3)	6	(0.6)	.483	.292
Neck stiffness	4	(0.6)	6	(0.6)	1.00	.928
Postnasal drip	4	(0.6)	6	(0.6)	1.00	.752
Seasonal allergy	4	(0.6)	6	(0.6)	1.00	.789
Syncope	0	(0.0)	6	(0.6)	.046	.024
Asthma NOS	2	(0.3)	5	(0.5)	.707	.606
Carbohydrate craving	2	(0.3)	5	(0.5)	.707	.309
Difficulty in micturition	0	(0.0)	5	(0.5)	.082	.085
Dysmenorrhoea	10	(1.4)	5	(0.5)	.063	.042
Early morning awakening	0	(0.0)	5	(0.5)	.082	.045
Eructation	1	(0.1)	5	(0.5)	.410	.201
Feeling cold	0	(0.0)	5	(0.5)	.082	.066
Feeling hot	0	(0.0)	5	(0.5)	.082	.045
Fungal infection NOS	3	(0.4)	5	(0.5)	1.00	.901
Haematuria	0	(0.0)	5	(0.5)	.082	.082
Joint sprain	2	(0.3)	5	(0.5)	.707	.681
Laryngitis NOS	0	(0.0)	5	(0.5)	.082	.045
Mydriasis	0	(0.0)	5	(0.5)	.082	.032
Nightmare	1	(0.1)	5	(0.5)	.410	.127
Tooth extraction NOS	1	(0.1)	5	(0.5)	.410	.264

Table C-7.A.1 Statistically Significant Mean Change from Baseline to Endpoint Laboratory Analytes

			Baseline		Change to Endpoint		p-Values	
Lab Test-Unit	Therapy	n	Mean	SD	Mean	SD	Therapy	Pair-wise
SODIUM mmol/L	PLA	668	140.5	2.6	0.1	2.9	.003	
	DLX	950	140.6	2.6	-0.3	2.9	(.006)	.003
POTAS mmol/L	PLA	668	4.27	0.41	0.02	0.44	.109	
	DLX	949	4.29	0.40	-0.01	0.42	(.396)	.109
CHLOR mmol/L	PLA	668	103.9	2.7	0.6	2.9	<.001	
	DLX	950	103.9	2.7	-0.1	2.9	(.045)	<.001
UR AC umol/L	PLA	668	288.4	86.6	2.1	45.7	<.001	
	DLX	950	296.4	79.0	-8.8	43.8	(.745)	<.001
CHOL mmol/L	PLA	668	5.203	1.049	-0.110	0.585	.005	
	DLX	950	5.273	1.039	0.004	0.630	(.969)	.005
PHOS mmol/L	PLA	668	1.168	0.186	-0.016	0.197	.036	
	DLX	950	1.171	0.175	-0.026	0.202	(.327)	.036
HCT	PLA	555	0.4115	0.0346	-0.0017	0.0268	.006	
	DLX	815	0.4128	0.0342	0.0001	0.0258	(.018)	.006
HGB mml/L Fe	PLA	556	8.696	0.776	-0.083	0.457	.021	
	DLX	820	8.697	0.778	-0.035	0.459	(.252)	.021
BICARB mmol/L	PLA	668	25.70	2.50	-0.30	2.67	.003	
	DLX	949	25.84	2.61	0.19	2.91	(.431)	.003

From NDA-21-427 Table ISS.2.2.12

Table C-7.2 Crtiteria for PCS Changes in Laboratory Analytes

Laboratory Condition			
(ALT/SGPT) test results >2X UL normal range			
(AST/SGOT) test results >3X UL normal range			
Total bilirubin >1.5X UL normal range			
Patients with bilirubin >1.5X UL normal and either ALT/SGPT >2X or AST/SGOT >3X UL normal range			
Analyte	**Units**	**Low Limit**	**High Limit**
AST/SGOT	U/L		150.000
ALT/SGPT	U/L		165.000
CPK:			
Female	U/L		507.000
Male	U/L		594.000
Alkaline Phosphatase	U/L		420.000
GGT:			
Female	U/L		135.000
Male	U/L		195.000
Urea Nitrogen	mmol/L		10.7100
Creatinine	µmol/L		176.800
Calcium	mmol/L	1.74650	2.99400
Inorganic Phosphorous	mmol/L	0.48435	1.77595
Sodium	mmol/L	129.000	160.000
Total Protein	g/L	50.0000	
Albumin	g/L		25.0000
Glucose (nonfasting)[a]	mmol/L	2.49750	11.1
Uric Acid:			
Female	µmol/L		505.580
Male	µmol/L		624.540
Total Cholesterol[a]	mmol/L		7.76
Total Bilirubin	µmol/L		34.2000
Hematocrit:			
Female	1	0.32000	0.50000
Male	1	0.37000	0.55000
Hemoglobin:			
Female	mml/L (Fe)	5.89570	10.2399
Male	mml/L (Fe)	7.13690	11.4811
Erythrocyte Count	TI/L	3.00000	6.00000
Leukocyte Count	GI/L	2.80000	16.0000
Platelet Count	GI/L	75.0000	700.000
Neutrophils, Segmented %	WBC	15.0000	
Eosinophils %	WBC		10.0000
UA-Specific Gravity		1.00100	1.03500
UA-pH		4.60000	8.00000
UA-RBC			inc. ≥2 + score ≥3
UA-WBC			inc. ≥2 + score ≥3
UA-Casts, Hyaline			inc. ≥2 + score ≥3
UA-Protein			inc. ≥2 + score ≥3
UA-Ketones			inc. ≥2 + score ≥3
UA-Glucose			inc. ≥2 + score ≥3

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/s/

Paul Andreason
8/16/02 02:07:25 PM
MEDICAL OFFICER

Thomas Laughren
8/19/02 10:13:15 AM
MEDICAL OFFICER
I agree that this NDA is approvable; see memo to file for more detailed comments.--TPL