Meeting of the Advisory Committee for Reproductive Health Drugs

June 18, 2010

Scott Monroe, MD

Director, Division of Reproductive and Urologic Products

Flibanserin

(5-HT_{1A} receptor agonist / 5-HT_{2A} receptor antagonist)

Boehringer Ingelheim

NDA 022526

Proposed Indication

Treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women

Hypoactive Sexual Desire Disorder (HSDD)

- Definition of HSDD based on criteria listed in DSM-IV-TR
  - Deficiency or absence of sexual fantasies and desire for sexual activity
  - Causes marked distress or interpersonal difficulty
  - Not better accounted for by a general medical, other psychiatric, or a substance- or drug-related condition
- Development of safe and effective medical therapies has posed challenges for both the Agency and Industry
  - Selection of meaningful efficacy endpoints
  - Developing and validating instruments to assess endpoints
- No FDA-approved medical therapy for HSDD

Hypoactive Sexual Desire Disorder (HSDD)

- FDA draft Guidance (2000) for development of drugs for treatment of female sexual dysfunction, including HSDD
  - Provides general guidance
  - Treatment effect should be both statistically significant and clinically meaningful
  - Primary endpoint: satisfactory sexual events (SSEs)
- Sponsors also advised that endpoints should include
  - Change in sexual desire (co-primary endpoint)
  - Change in distress related to HSDD (key 2nd endpoint)
- Instruments to assess endpoints selected by Sponsor but need to be validated by Sponsor and agreed-to by Division

Assessment of Primary Endpoints

- Applicant and FDA agreed on use of an electronic diary (eDiary) to record SSEs and desire on a daily basis
- Applicant requested to use another instrument to assess desire after analysis of the first phase 3 study, in which eDiary desire endpoint was not statistically significant
  - desire domain questions on the Female Sexual Function Index (FSFI)
  - FSFI administered once a month at clinic visits
- Applicant stated that several factors, e.g., poor compliance with daily data entry and the daily recall requirement, limited the utility of eDiary to assess changes in desire

Questions for the Committee

- Considering that the two primary US efficacy studies did not demonstrate efficacy for the prespecified co-primary endpoint of sexual desire as measured by the daily eDiary:
  - Do you agree with the Applicant that the impact of flibanserin on sexual desire is better evaluated with the desire domain of the FSFI using 28-day recall?
  - Is it appropriate to alter the prespecified method of assessing sexual desire?

Questions for the Committee

- Has the Applicant provided sufficient evidence of overall efficacy for flibanserin for the treatment of hypoactive sexual desire disorder (HSDD) compared to placebo?
- Considering the available data on efficacy and safety, has the Applicant demonstrated that the overall risk/benefit profile of flibanserin for the treatment of HSDD in premenopausal women is acceptable?

Agenda

8:25	Boehringer Ingelheim Presentation
9.55	Break
10:05	FDA Presentation
11:05	Questions from the Committee
12:15	Lunch
1:00	Open Public Hearing
2:00	Committee Discussion and Voting
3:30	Adjournment

Efficacy of Flibanserin for Treatment of Hypoactive Sexual Desire Disorder (HSDD) in Premenopausal Women

Daniel Davis, MD, MPH
Division of Reproductive and Urologic Products (DRUP)

June 18, 2010

Overview

- First application for this class of drug for HSDD
  - No FDA-approved drug for HSDD
- **Acquired HSDD**- low sexual desire causing personal distress; previously normal desire and fantasies
- Overview of the clinical development program
- Efficacy trial design, inclusion/exclusion criteria, key endpoints and instruments
- Analysis plan, the efficacy findings and issues
- Safety findings and issues: Drs. Easley and Lee

Clinical Development Program

- FDA Draft Guidance for FSD and DRUP advice followed
  - Primary endpoints are change from baseline in the number of satisfactory sexual events (SSEs) and in sexual desire
  - Key secondary endpoint: change in distress due to HSDD
  - Need to show the clinical significance of the results
- Instruments used to assess efficacy
  - eDiary (electronic) for recording SSEs and sexual desire score
  - Female Sexual Distress Scale (FSDS-R) for change in distress due to HSDD
  - Patient Global Impression of Improvement (PGI-I)

HSDD Clinical Studies

- 7 bioavailability studies
- 15 pharmacokinetic (PK)
- 6 pharmacodynamic (PD)
- 7 validation studies
- HSDD efficacy/safety studies: two phase 2 and seven phase 3
- Three trials with the proposed 100 mg qhs
  - **Two US (511.71 and 511.75) studies**
  - **One European study (511.77)**

Trial Design 511.71 and 511.75

- Randomized, double-blind, placebo arm
- 4-wk baseline for all HSDD parameters
- 24-wk blinded treatment period
  - eDiary daily collected and downloaded daily
  - FSDS-R at clinic visits (Wk 0, 4, 8, 16, 24)
  - FSFI at clinic visits (Wk 0, 4, 8, 16, 24)
  - PGI-Improvement (Wk 4, 8, 16, 24)
- Final visit 4-wk post treatment (Wk 28)

Key Inclusion-Exclusion Criteria

- Healthy premenopausal women
  - age18 and above
  - using reliable contraception
  - in a stable heterosexual relationship
- HSDD diagnosed by expert person
  - In-depth interview
  - Instruments were used to determine receptivity and sexual enthusiasm, distress, and rule out depression
  - HSDD for at least 24 weeks
- Five page list of prohibited medications

Primary and Secondary Endpoints

- Primary endpoints (change from baseline values)
  - *Satisfactory sexual events* (SSEs) during last 4 weeks
  - *Sexual desire score* during the last 4-week's daily eDiary data
- Key secondary endpoint
  - Change from baseline in the *total distress score* on the Female Sexual Distress Scale (FSDS-R)
- Other secondary endpoints (exploratory)
  - Change in Female Sexual Function Index (FSFI) *sexual desire score* (2 questions)- Trial 511.71 only
  - Change in FSDS-R item 13 (distressed by low sexual desire)

Instruments Used

- eDiary for SSEs and sexual desire
  - Up to a 72-hour window to record SSEs
  - 24-hour window to record a desire score of none, low, moderate, or strong
    - 0 to 3 scale x 28 day; 0-84 range for 4 weeks
  - Validation studies were done

Instruments Used

- **Female Sexual Distress Scale-Revised: FSDS-R**
  - 13 questions on various aspect of distress
  - 0-4 scale (never to always); 0-52 range
  - Higher score means ↑ distress; want ↓ score
  - Division preferred item 13 alone: “How often did you feel bothered by low sexual desire?”
  - Adapted for 7-day recall used in 2 studies

Instruments Used

- **Patient Global Impression of Improvement: PGI-I**
  - "How is your condition- meaning decreased sexual desire and feeling bothered by it- today compared to when you started study medication?"
  - 1= very much improved to 7= very much worse
    - 3= minimally improved; 4 = no change

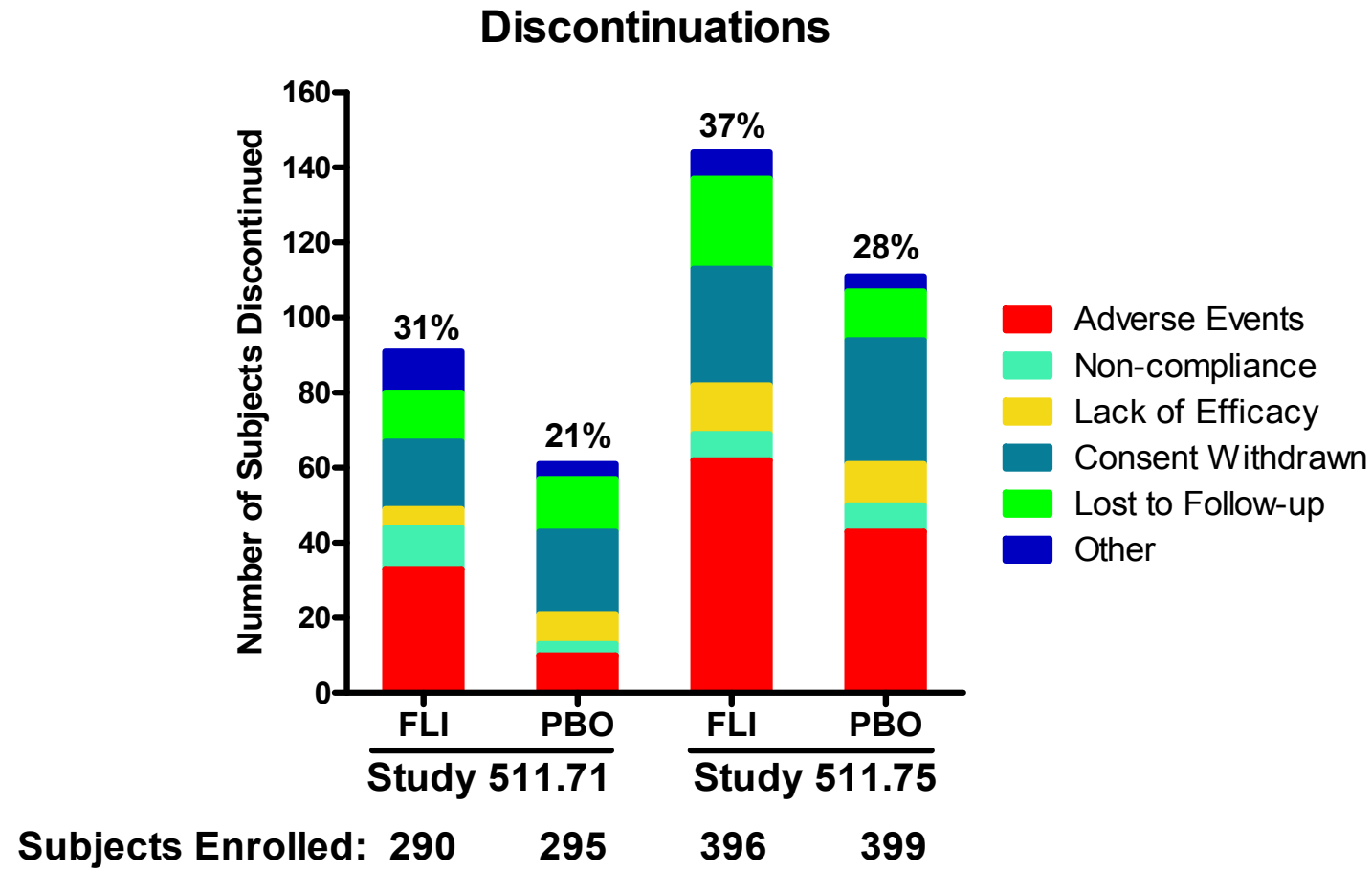
Statistical Analysis Plan

- Analysis population: full analysis set (FAS) with last observation carried forward (LOCF)
- Must win first on SSEs, then change in sexual desire
- Key Secondary endpoint: FSDS-R total score (511.71 and 511.75)

Demographics: 511.71 & 511.75

- Average age 35-36
  - Age 18-34: 44%
  - Age 35-44: 43-46%
- Race:
  - Caucasian 80-86%
  - Hispanic 5-8%
  - African-American 7-11%
  - Asian 2%
- Married 78%; present partner 10+ years
- HS grad 99%; college or more 55-60%

Discontinuations: 511.71 and 511.75



Satisfactory Sexual Events

	Baseline	End of Treatment	Change	Placebo corrected	p-value
Study 511.71 N ≈ 293/arm					
FLI	3.0	4.6	1.6	0.8	0.005
Placebo	2.7	3.5	0.8	-----	-----
Study 511.75 N ≈ 395/arm					
FLI	2.6	4.4	1.9	0.8	0.024
Placebo	2.7	3.7	1.1	-----	-----

eDiary Sexual Desire Score

	Baseline	End of Treatment	Change	Placebo corrected	p-value
Study 511.71 **N ≈ 293/arm**					
FLI	12.9	21.2	9.1	2.2	0.132
Placebo	11.8	18.1	6.9	-----	-----
Study 511.75 **N ≈ 395/arm**					
FLI	12.0	20.1	8.5	1.7	0.346
Placebo	10.2	16.9	6.8	-----	-----

Maximum score is 84 for 28 days: 0-3 scale each day

Personal Distress Total Score

	Baseline	End of Treatment	Change**	Placebo corrected	p-value*
Study 511.71 N≈ 285/arm					
FLI	30.7	21.6	-8.9	-3.9	<0.001
Placebo	30.1	25.2	-4.9	-----	-----
Study 511.75 N≈ 385/arm					
FLI	30.6	22.9	-7.8	-2.5	<0.001
Placebo	30.2	25.3	-5.2	-----	-----

*Not adjusted for multiple comparisons and multiple endpoints
** Least Square means: ANCOVA (FAS,LOCF)- Applicant data
Maximum score is 52 for 13 items: 0-4 scale each day

Issues in the Assessment of Desire

- Female Sexual Function Index (FSFI)
  - 6 domains with19 items; total score has a 2-36 range
  - **28 day recall**; 2 desire questions
  - Applicant elevated FSFI desire items to key secondary endpoint in Study 511.71; DRUP did not concur
  - FDA advice (Jan 2009):
    - Proposal to alter the instrument used for the co-primary desire endpoint is not acceptable for Studies 71 and 75; these data considered exploratory and hypothesis-generating
    - Would need to be confirmed in another study using pre-specified FSFI desire endpoint
    - If SSEs are significant in that study, and FSFI appropriately validated, then may use FSFI to assess change in sexual desire
- European study (6-mo, DB, PC) revised protocol used the FSFI as pre-specified key secondary endpoint with SSEs as the primary endpoint

European Study Efficacy

Treatment N~300/arm	Baseline	End of Treatment	Change	Placebo corrected	p-value
SSEs					
FLI	2.4	3.9	1.5	0.6	0.140***
Placebo	2.3	3.1	0.9	-----	-----
FSFI Desire					
FLI	1.9	2.5	0.7**	0.1**	0.082*
Placebo	1.9	2.3	0.5**	-----	-----
N~310/arm	**eDiary Desire**				
FLI	9.5	16.1	7.7**	2.3	0.024*
Placebo	9.1	13.2	5.4**	-----	-----

*ANCOVA (FAS, LOCF); **LS Mean; *** Wilcoxon Rank Sum test

Responder Values

Study	SSE	Desire – eDiary	Distress – FSDS-R Total score
511.71	1.22	7.80	-5.63
511.75	1.25	7.91	-5.07

7 PGI-I Responses from 1= very improved to 7= very much worse

Responder Rates 511.71

Responder endpoint %	FLI 100 qhs	Placebo	Delta	p-value**
SSE	47.6	33.0	14.6	<0.001
eDiary desire	41.1	38.2	2.9	0.492
FSDS-R total	55.7	43.9	11.8	0.006

**Not adjusted for multiple comparisons and multiple endpoints

Responder Rates 511.75

Responder endpoint %	FLI 100 qhs	Placebo	Delta	p-value**
SSE	44.2	34.1	10.1	0.005
eDiary desire	38.0	32.0	6.0	0.064
FSDS-R total	52.1	40.9	9.2	0.001

**Not adjusted for multiple comparisons and multiple endpoints

Clinical Efficacy Summary

- Statistically significant increase in mean number of SSEs
  - Flibanserin (placebo corrected) = 0.8 events per 4 weeks
  - Responders (placebo corrected) = 10 to 15%
- **Non-significant** treatment effect in mean change in eDiary sexual desire score
  - Flibanserin (Placebo corrected) = 2.2 and 1.7
  - Responders (placebo corrected) = 3 to 6%
- Statistically significant treatment effects in distress using item 13 on the FSDS-R
  - Distress Score: Flibanserin (Placebo corrected) = -0.4 and -0.3
  - Responders (placebo corrected) = 9 to 12%

Key Efficacy Issues

- Sexual desire efficacy results and the instruments used
  - eDiary versus FSFI's 2 desire items
  - daily vs. 28-day recall
- Appropriateness of modifying the analysis plan after study completion/unblinding
- Is there sufficient evidence of overall efficacy of flibanserin compared to placebo for the treatment of HSDD?

Safety of Flibanserin for the Treatment of HSDD in Pre-menopausal Women

Olivia J. Easley, M.D.
Medical Officer
Division of Reproductive and Urologic Products (DRUP)

Safety Concerns

- Overall tolerability of flibanserin
  - Women with co-morbidities
  - Concomitant medications
    - CNS-active prescription drugs
    - CYP3A4 inhibitors
- Specific adverse events
  - Accidental injury
  - Syncope
  - Depression

Flibanserin Safety Database

- Four phase 3 placebo-controlled HSDD studies (511.70, 511.71, 511.75, 511.77)
- Two open-label, 52-week safety extension studies (511.84, 511.118) in HSDD population
- A 48-week, phase 3 randomized withdrawal study in premenopausal females with HSDD (Study 511.74)
- Two phase 2 randomized trials in HSDD
- Nine phase 2 placebo-controlled trials in major depressive disorder (MDD)

Flibanserin Exposure (all HSDD trials)

Exposure (days)	25 bid N	50 qhs N	50 bid N	100 qhs N	100 bid N	Total N
≥1	814	3839	1257	2938	72	**5,018**
≥84	605	1255	666	2144	0	**3,850**
≥365	2	89	13	213	0	**1,130**
Subject years	297.5	925.8	364	1525.6	4.6	**3,117.5**

Deaths and Serious Adverse Events

- No deaths in any flibanserin-treated subject in entire HSDD or MDD database

Serious adverse events – Phase 2/3 placebo-controlled HSDD Trials					
Preferred term	**Placebo**	**25 mg bid**	**50 mg qhs**	**50 mg bid**	**100 mg qhs**
Total with SAEs (%)	0.5	0.5	0.6	0.3	0.9
Appendicitis (%)	0	0.1	0.2	0.1	0

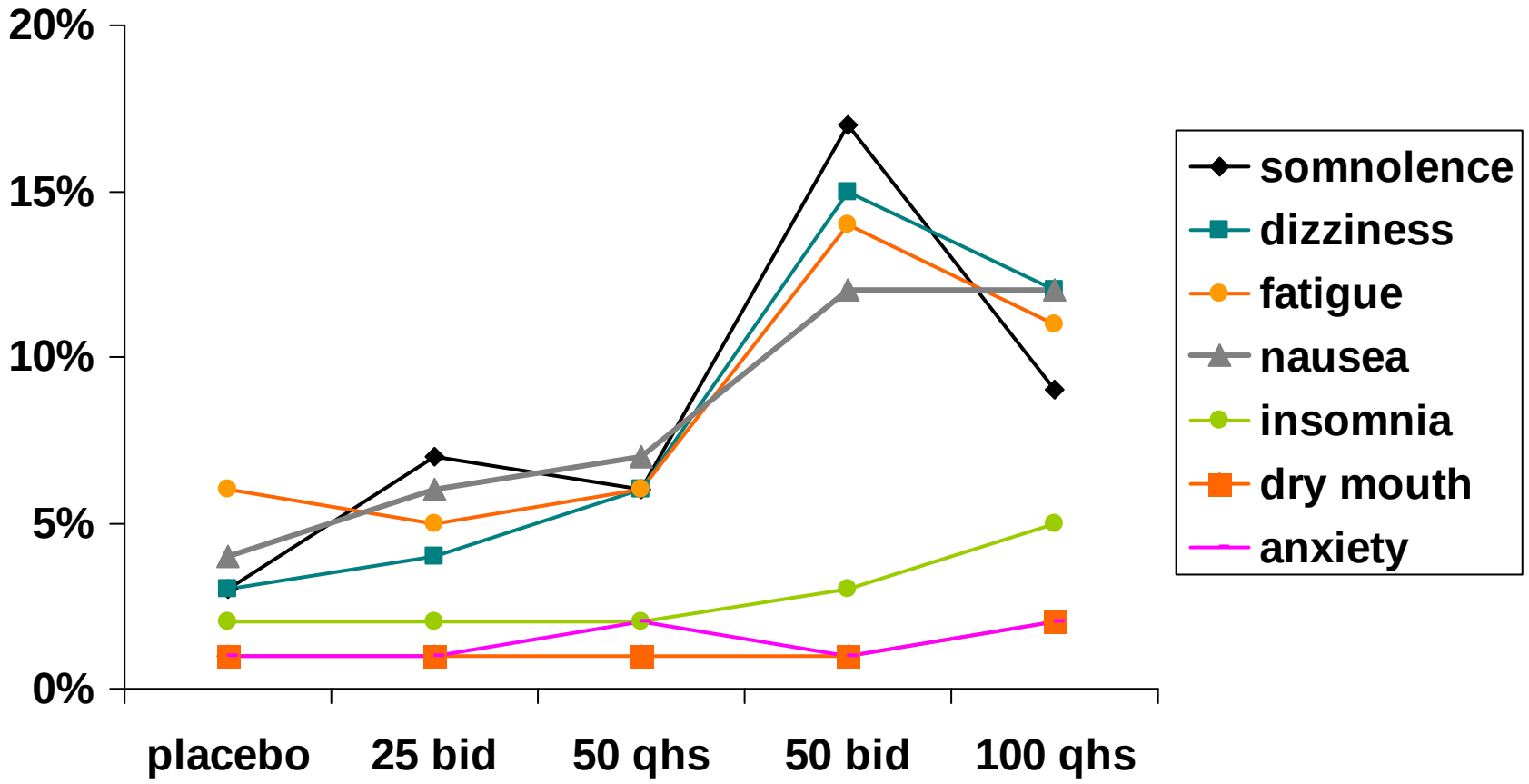
Treatment-Emergent Adverse Events

(Percentage of Subjects in phase 3 placebo-controlled HSDD trials)

	Placebo N=1,360	**25 mg bid N=733**	**50 mg qhs N=969**	**50 mg bid N=728**	**100 mg qhs N= 1,001**
Any event (%)	58	59	65	71	70

Common Treatment Emergent Adverse Events

(phase 3 placebo-controlled HSDD trials)

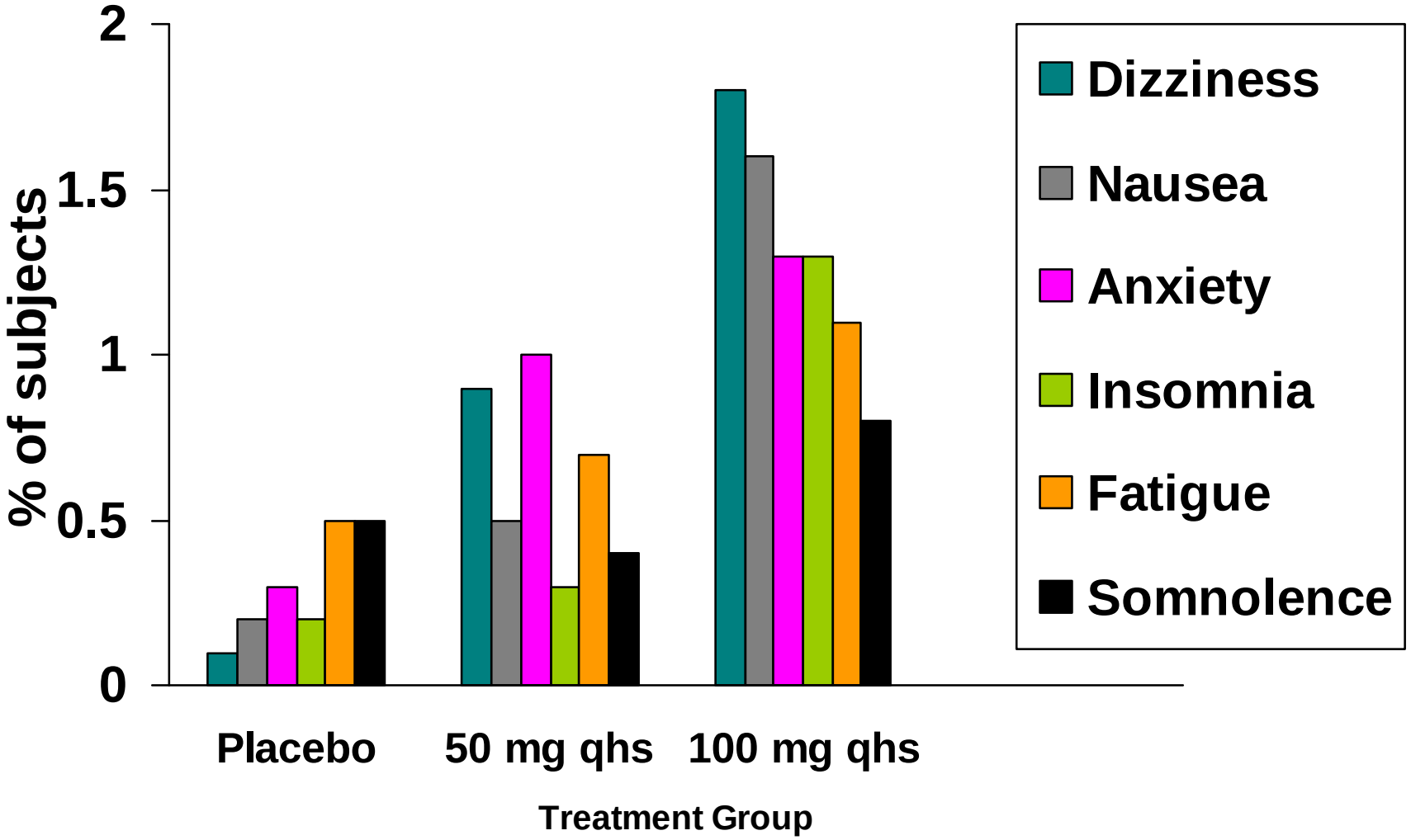


Treatment Discontinuation due to Adverse Events

(Percentage of subjects in phase 3, placebo-controlled HSDD trials)

	Placebo	50 mg qhs	100 mg qhs
Total N	**1,360**	**969**	**1,001**
% discontinued	7	10	15

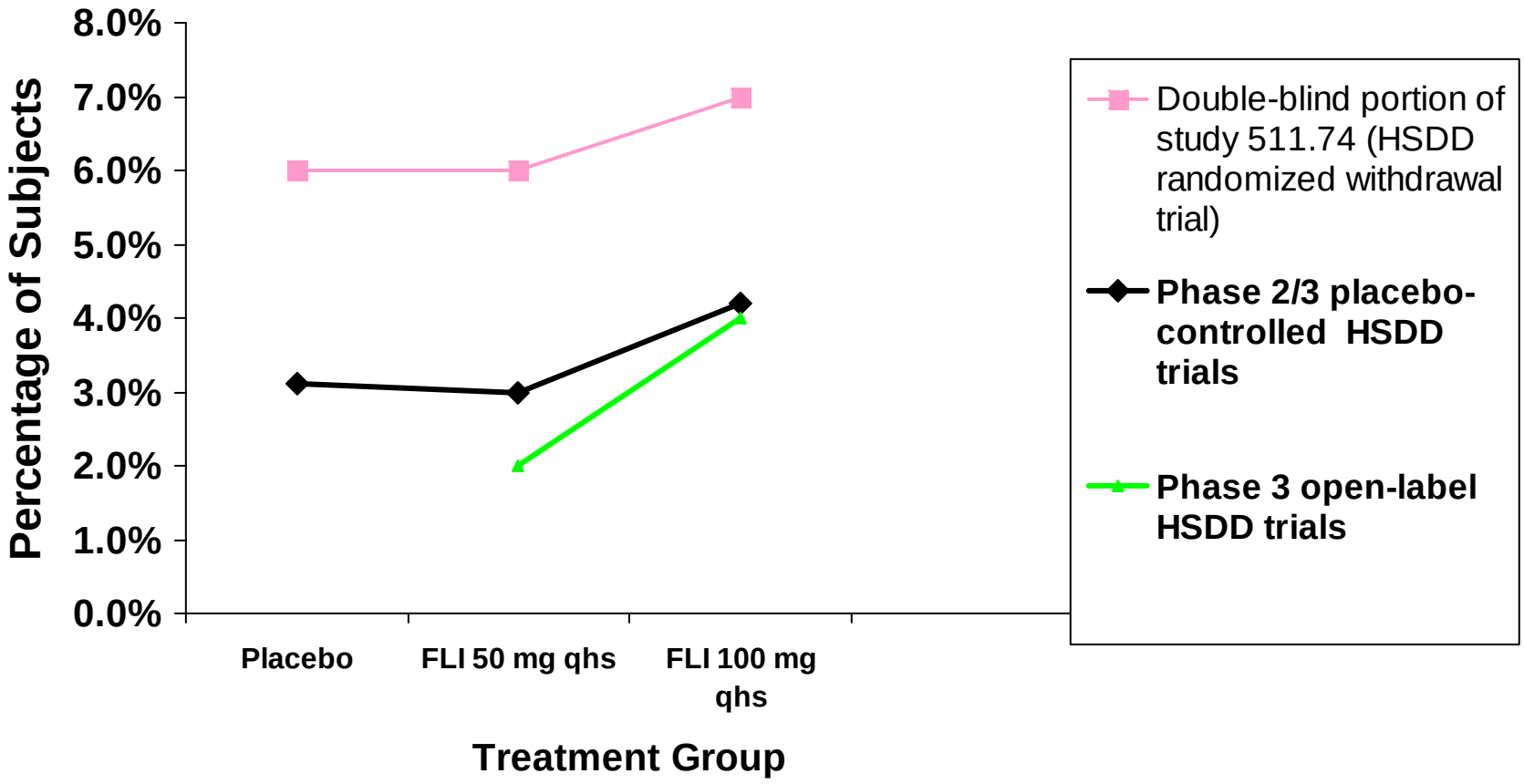
Adverse Events Leading to Treatment Discontinuation
(phase 3 placebo-controlled HSDD trials)



Safety issues of Particular Concern

- Depression
- Syncope
- Accidental Injury
- Suicidality (Division request)

Frequency of Depression in HSDD Database



Suicidality

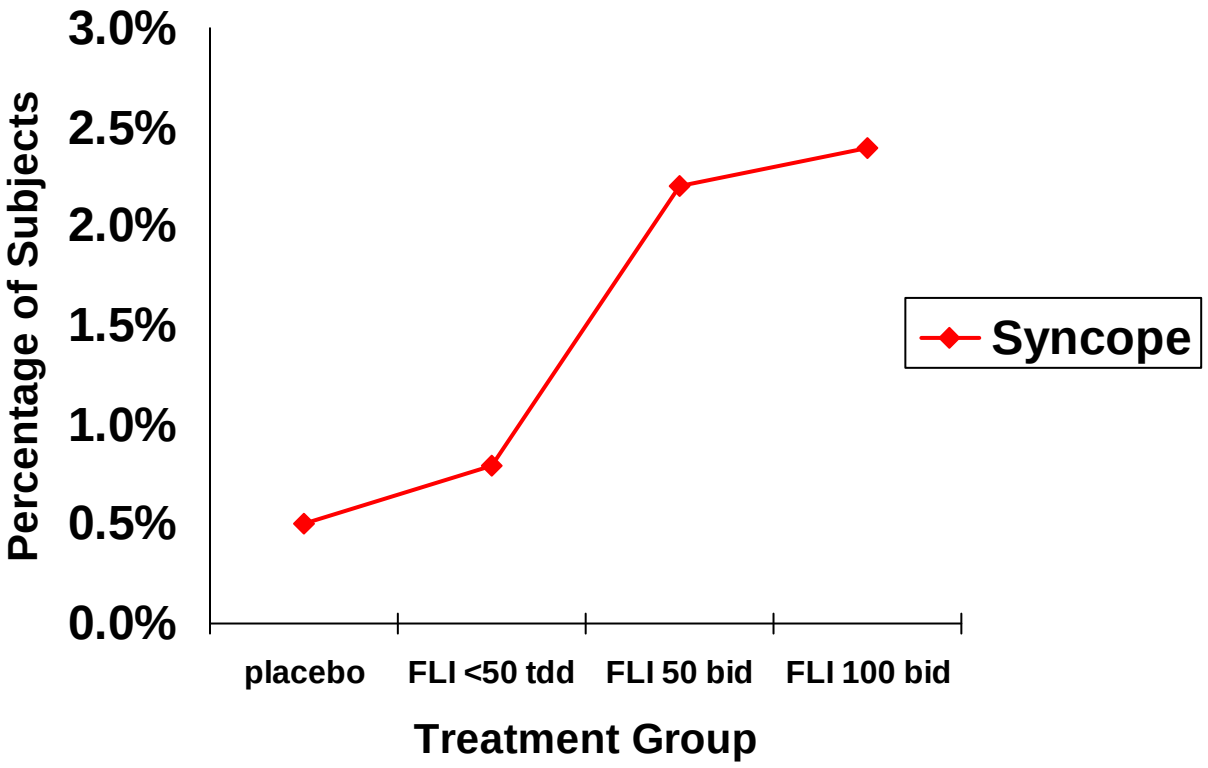
- No signal based on evaluation during treatment in phase 3 HSDD trials
- No increase in suicidality-related adverse events in HSDD database

Syncope – HSDD Trials

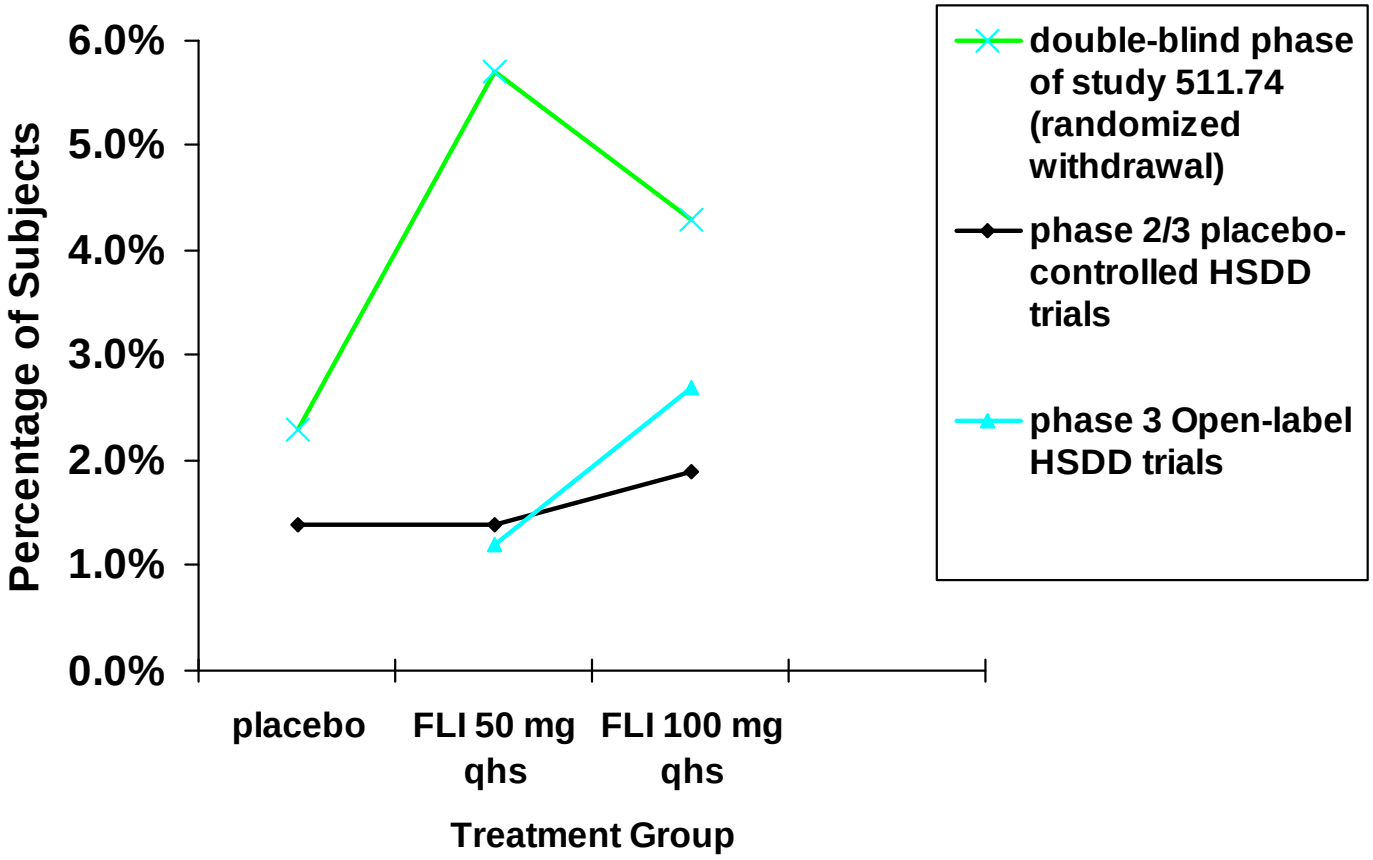
	Placebo	FLI 50 qhs	FLI 100 qhs
phase 2/3 placebo-controlled HSDD Trials			
Total N	1,508	2,072	978
Syncope (%)	0.3	0.3	0.7
Double-blind portion of study 511.74 (HSDD randomized withdrawal)			
Total N	170	35	115
Syncope (%)	1.1	0	1.7
phase 3 open-label HSDD trials (studies 511.84 and 511.118)			
Total N	NA	2,197	1,791
Syncope (%)	NA	0.3	0.6

Syncope - MDD database

(phase 2 placebo-controlled trials, female subjects only)



Accidental Injury – HSDD Database



Accidental Injury – MDD Database
(phase 2 placebo-controlled trials; female subjects only)

	Placebo	**FLI <50 tdd (total daily dose)**	**FLI 50 bid**	**FLI 100 bid (200 mg daily)**
Total N	417	240	313	113
Accidental injury (%)	2.2	0.8	1.6	3.5

Tolerability Of Flibanserin With Concomitant Medications Or Substances

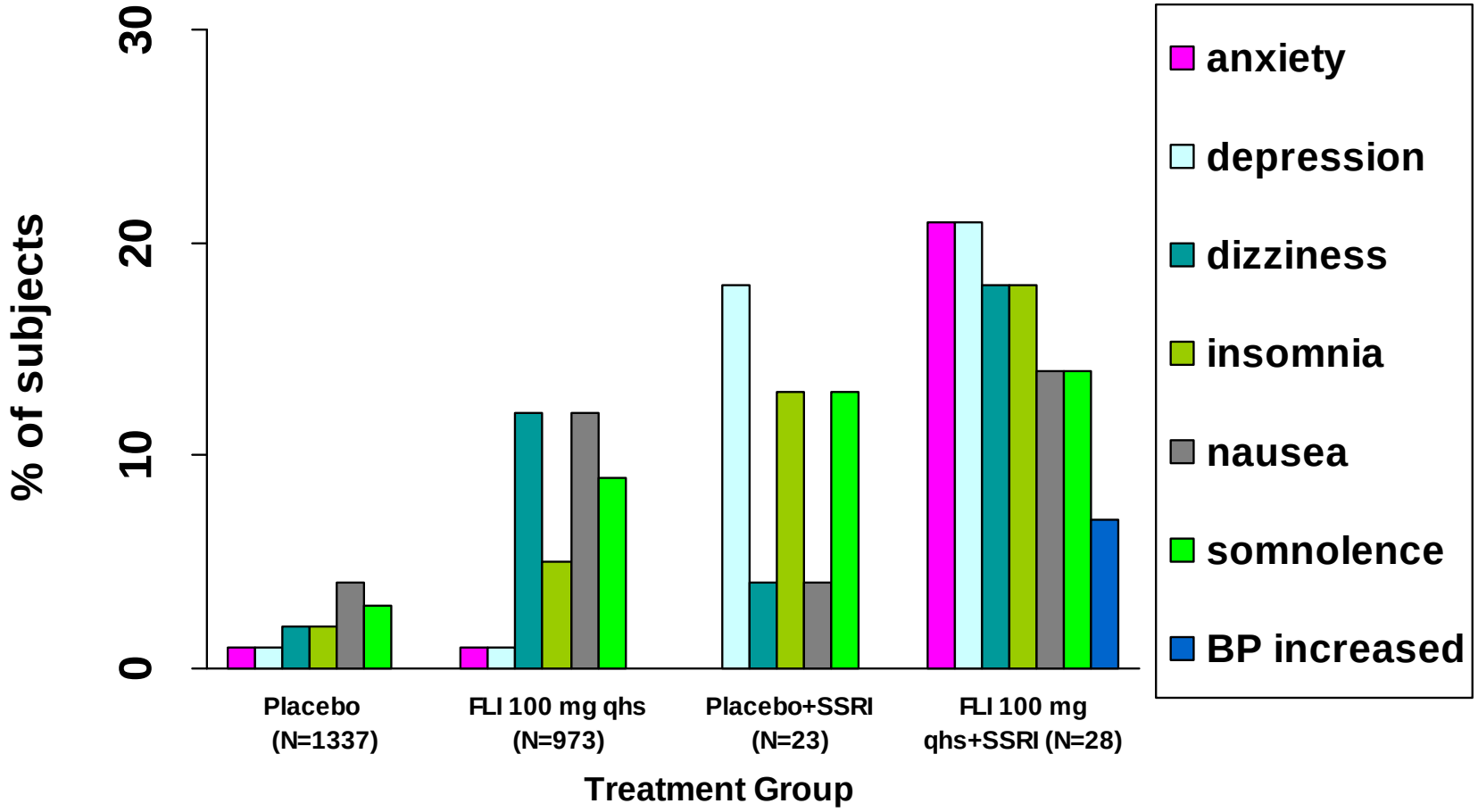
- Prescription drugs with CNS activity
  - Selective serotonin (or norepinephrine) reuptake inhibitors (SSRI/SNRI's)
  - Triptan anti-migraine agents
- Alcohol
- Potent CYP3A4 inhibitors

Flibanserin and Concomitant Medications

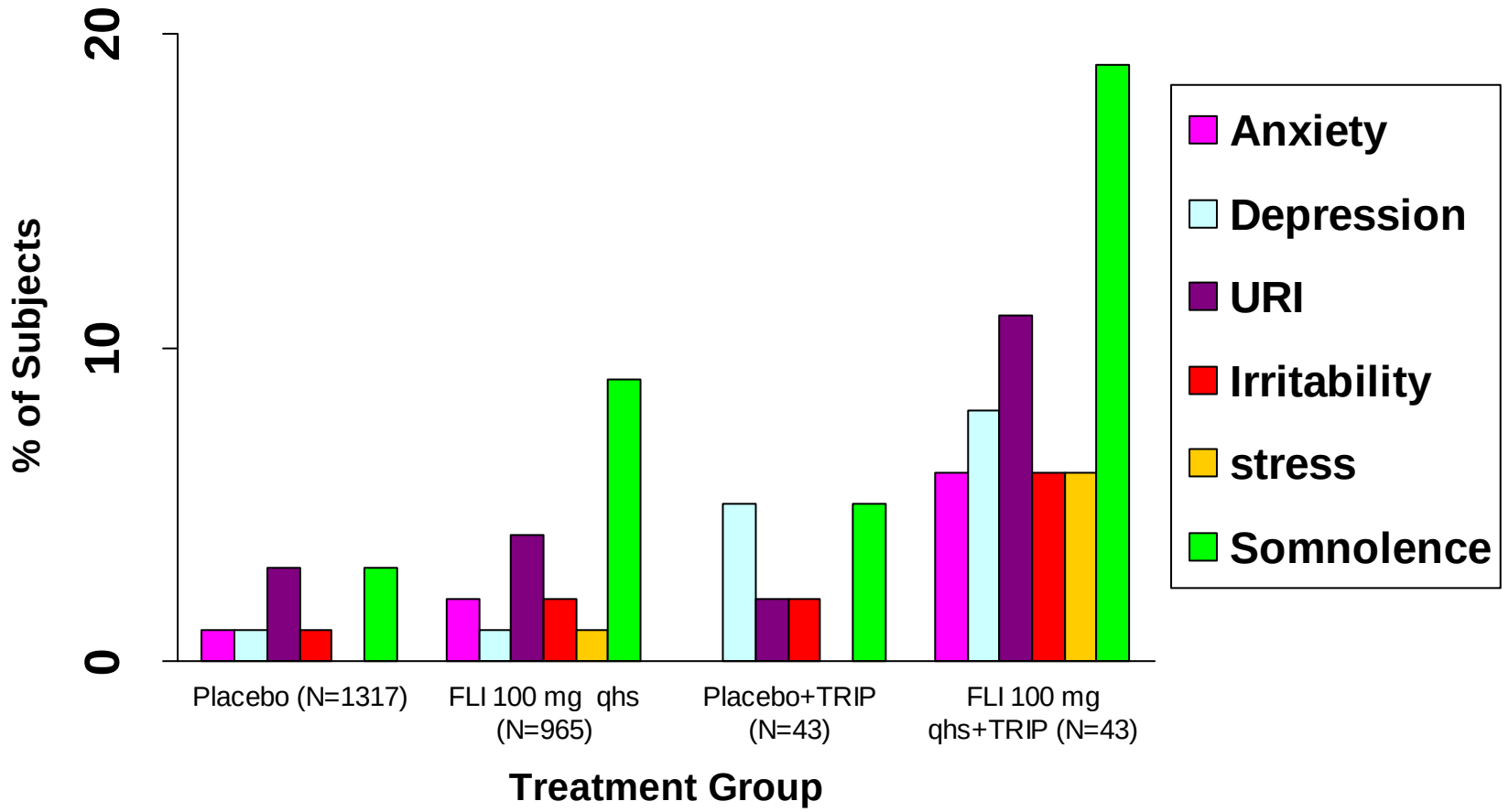
Medication Categories prohibited in Phase 2/3 trials:

- Anti-arrhythmics, anticoagulants, beta-blockers
- CNS stimulants, dopamine-receptor agonists
- All fertility drugs, all hormonal agonists/antagonists
- All muscle relaxants
- Psychotherapeutics
- Narcotics
- Triptan anti-migraine agents
- OTC sleep aids
- CYP3A4 inducers and inhibitors (except under special conditions)

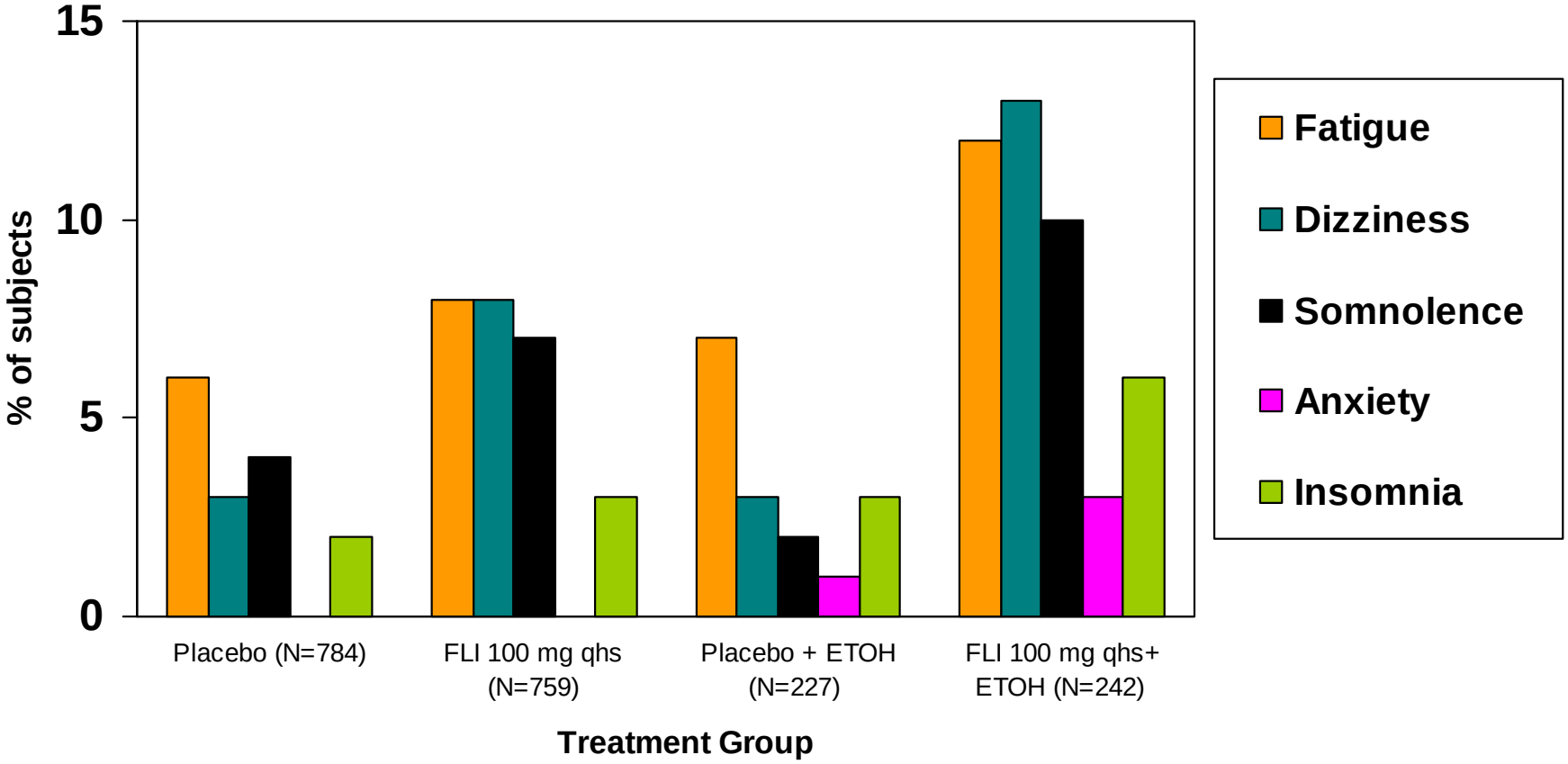
Flibanserin Tolerability With SSRI/SNRI's
(phase 3 placebo-controlled HSDD Trials)



Flibanserin tolerability with Triptans
(phase 3 placebo-controlled HSDD Trials)



Effect of Alcohol on frequency of adverse events
(phase 3 placebo-controlled HSDD trials)

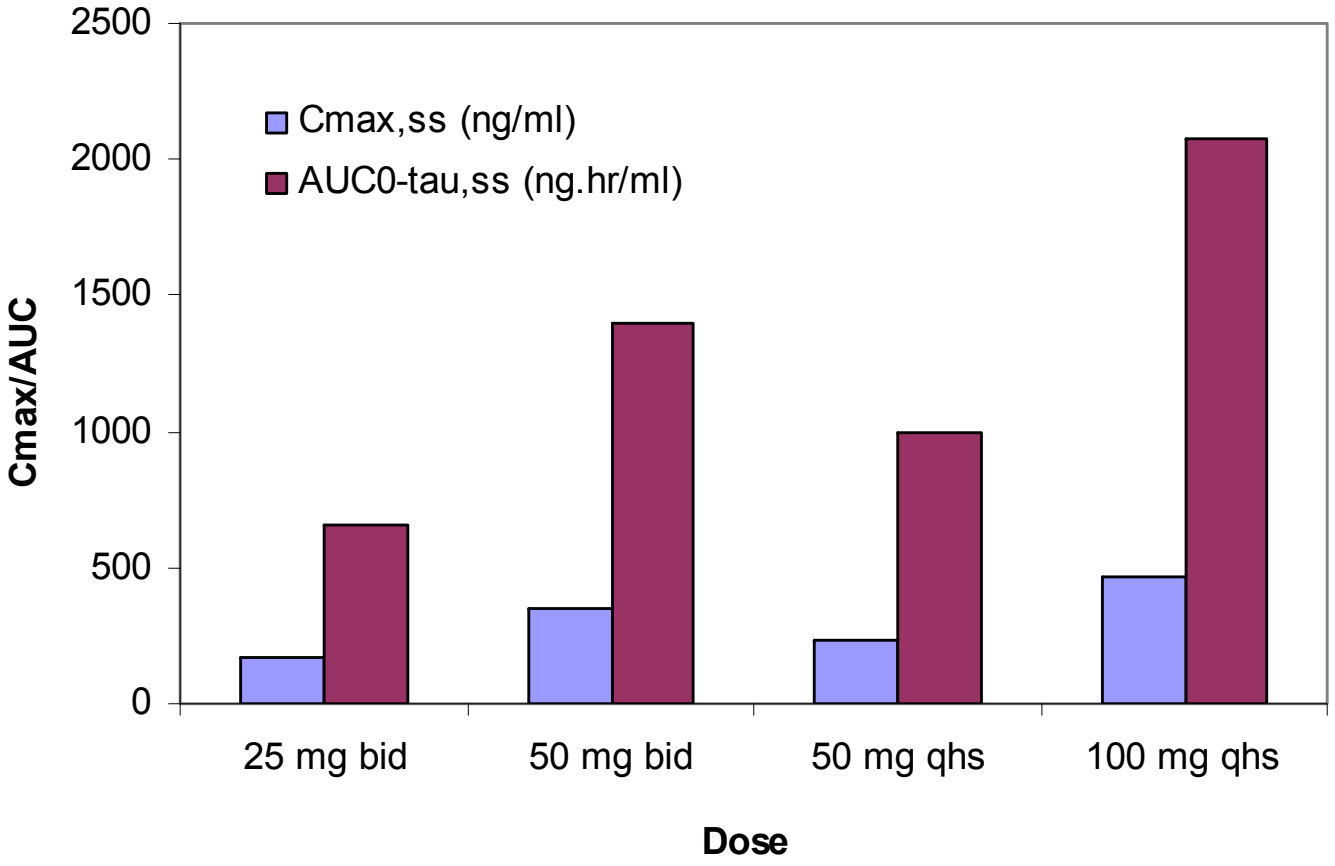


Effect of hepatic impairment and a strong CYP3A4 inhibitor on flibanserin exposure

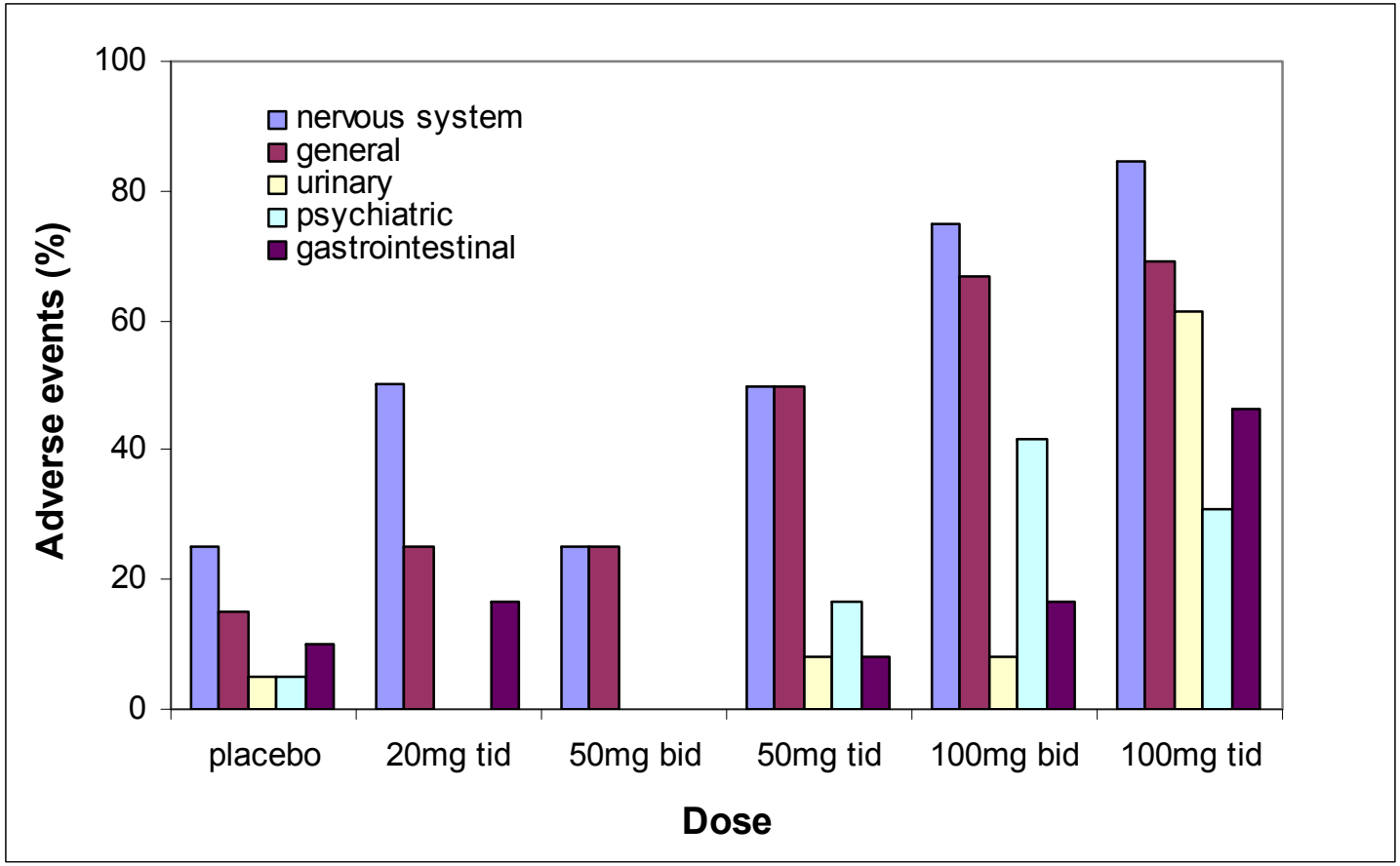
LaiMing Lee, Ph.D.
Office of Clinical Pharmacology
Division of Clinical Pharmacology 3

- Dose response (adverse events)
- Effect of hepatic impairment on flibanserin exposure
- Effect of a strong CYP3A4 inhibitor, ketoconazole, on flibanserin exposure

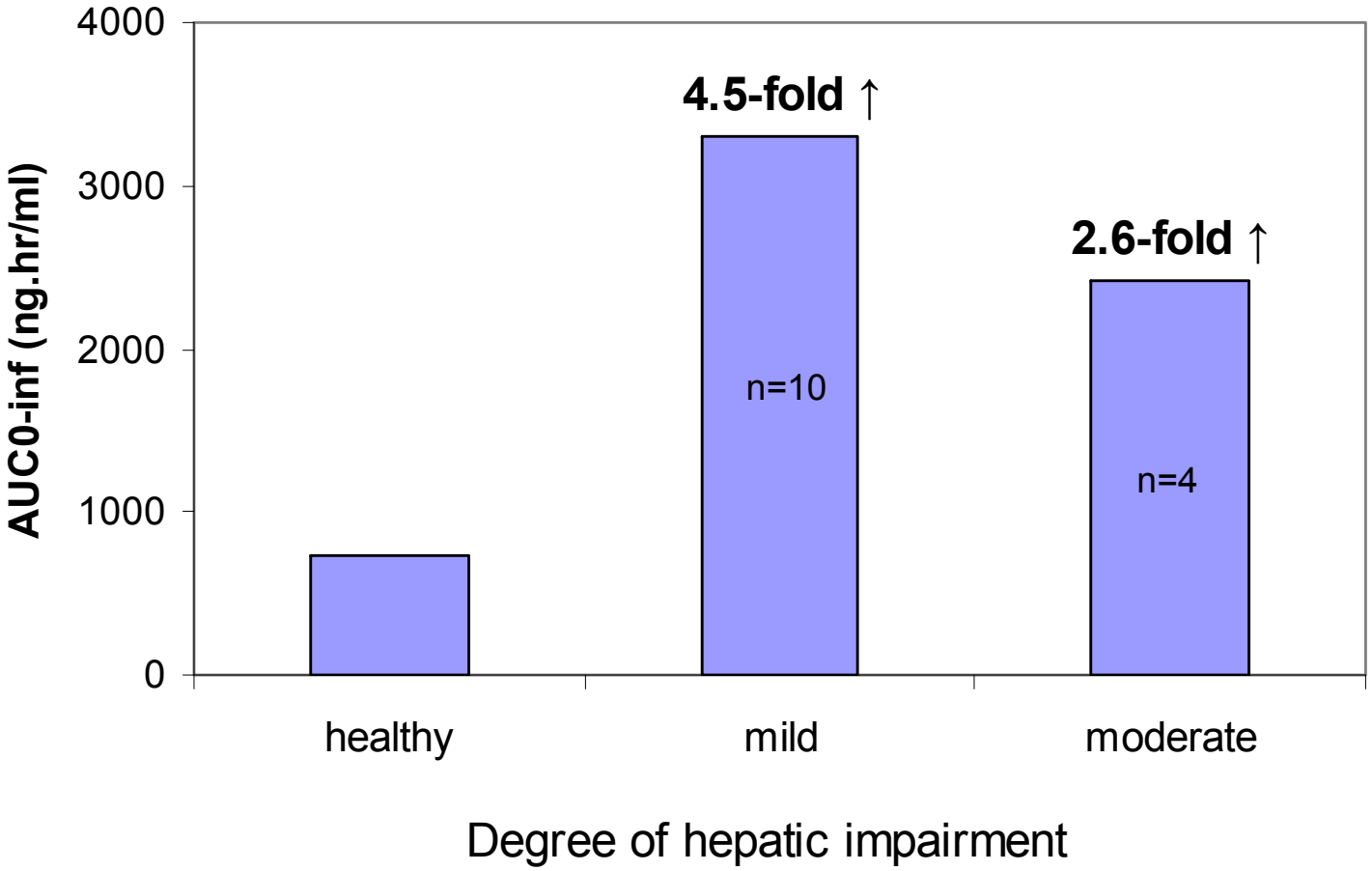
Pharmacokinetics of flibanserin in HSDD women (n=67)



Treatment-emergent adverse events in Phase 1 study

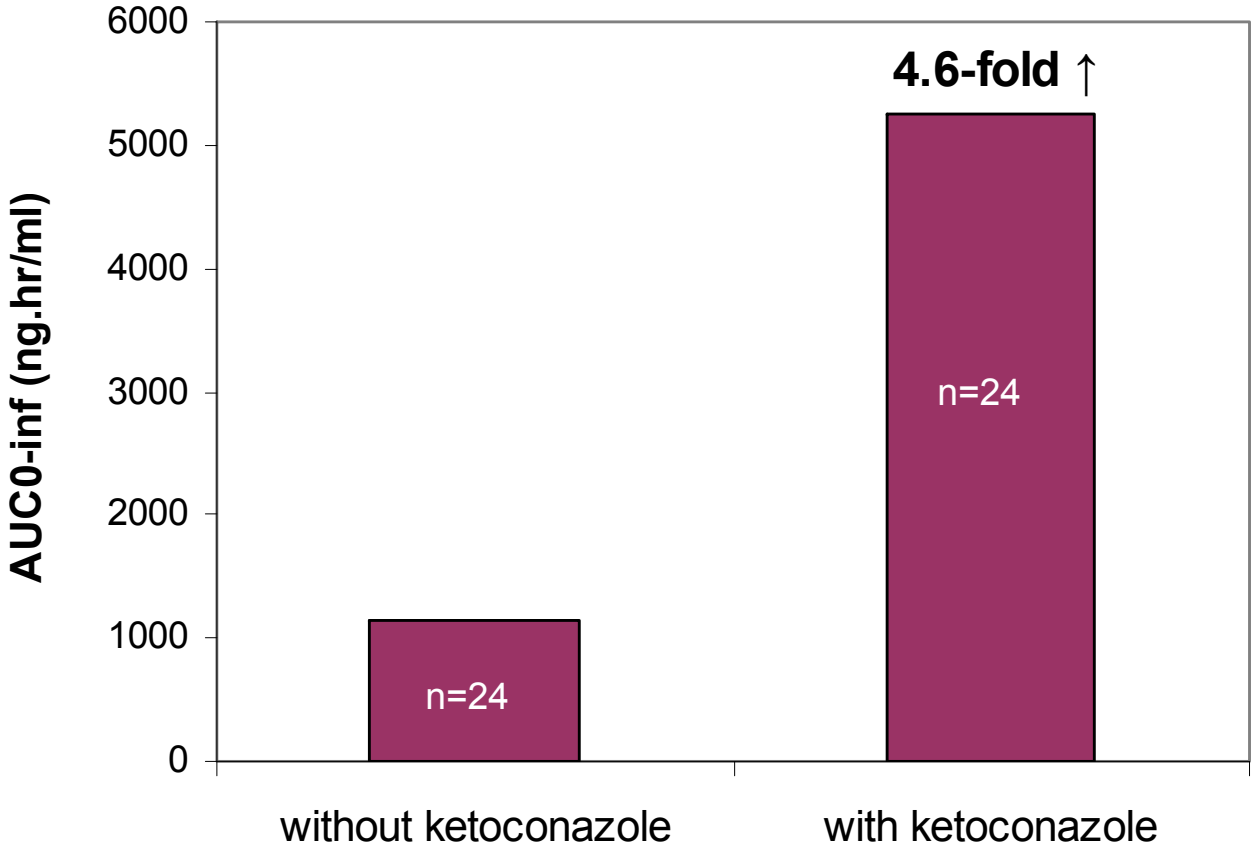


Effect of hepatic impairment



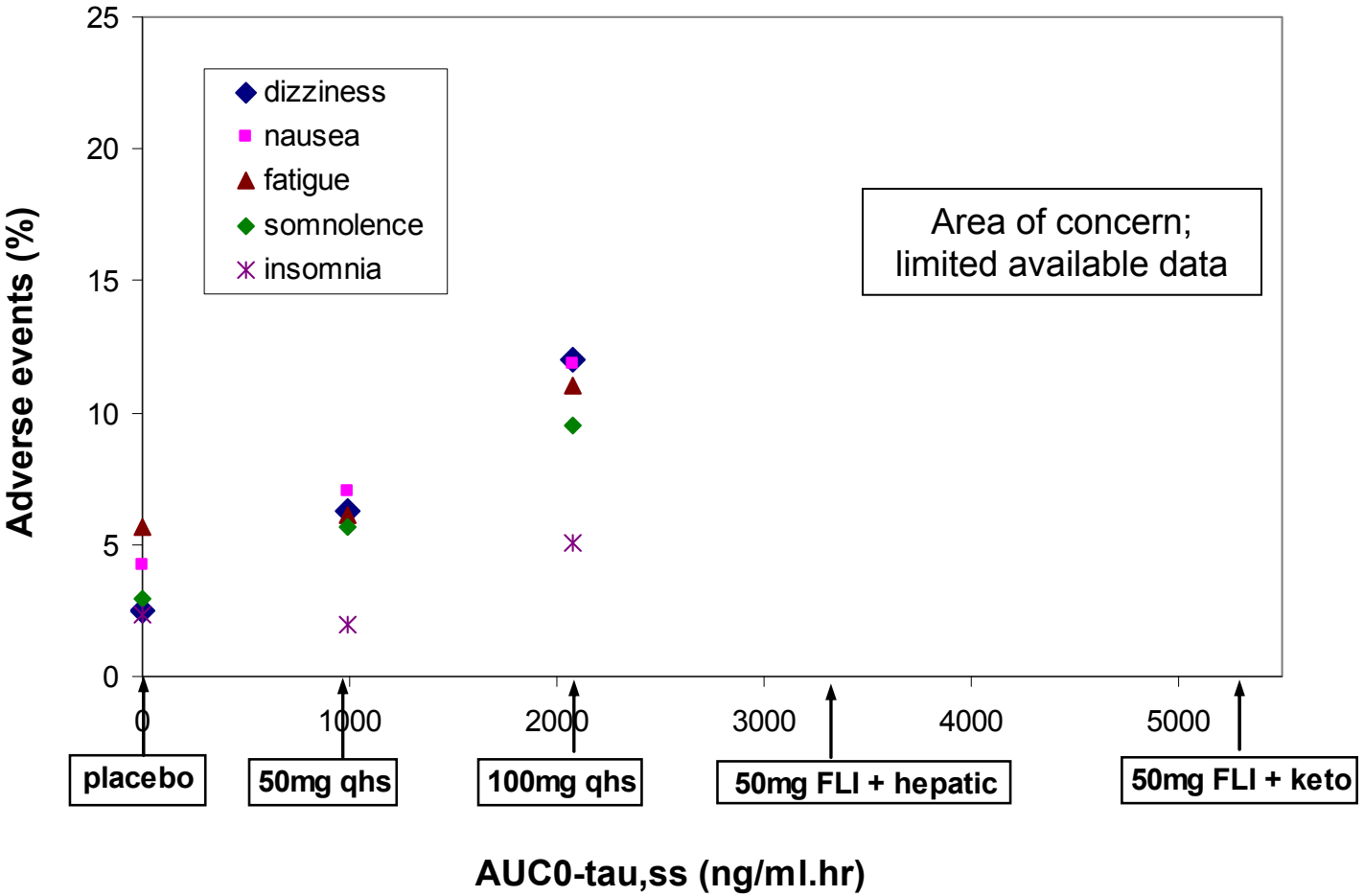
single dose flibanserin 50 mg

Effect of a strong CYP3A4 inhibitor



single dose flibanserin 50 mg

Effect of hepatic impairment and CYP3A4 inhibition on flibanserin exposure



Safety Conclusions

- 15% discontinuation rate for flibanserin (100 mg qhs) due to side effects
- Dizziness and nausea are the most frequently reported adverse events in flibanserin-treated subjects
- Sedating adverse events dose-proportional
- Small increase in frequency of depression, syncope, accidental injury with doses of flibanserin $\geq$100 mg qhs vs. placebo

Safety Conclusions (continued)

- Adverse effect of SSRIs, triptans, alcohol on flibanserin tolerability

- CYP3A4 inhibitors: marked increase in flibanserin exposure and poor tolerability

DRUP's Concerns Regarding Flibanserin Safety

- Safety and tolerability of flibanserin in patients with co-morbidities (medical, psychiatric) or on concomitant medications
- Potential risk associated with supra-therapeutic flibanserin exposure
- Potential for numerous drug interactions
- Overall risk/benefit of flibanserin for HSDD

Flibanserin: Question No. 1

- Considering that the two primary US efficacy studies did not demonstrate efficacy for the prespecified co-primary endpoint of sexual desire as measured by the daily eDiary:
  - Do you agree with the Applicant that the impact of flibanserin on sexual desire is better evaluated with the desire domain of the FSFI using 28-day recall?
  - Is it appropriate to alter the prespecified method of assessing sexual desire?

(Vote)

Flibanserin: Question No. 2

- Has the Applicant provided sufficient evidence of overall efficacy for flibanserin for the treatment of hypoactive sexual desire disorder (HSDD) compared to placebo?

  (Vote)

Flibanserin: Question No. 3

- Considering the available data on efficacy and safety, has the Applicant demonstrated that the overall risk/benefit profile of flibanserin for the treatment of HSDD in premenopausal women is acceptable?

  (Vote)