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Lorcaserin: Receptor Pharmacology, Selectivity, and Toxicology

Arena Pharmaceuticals
NDA 22-529

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

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Outline

- 1. Serotonin Receptor Selectivity of lorcaserin**
- 2. Preclinical evaluation of Neurological and Cardiac toxicity**
- 3. Tumor findings in Rodents (Dr. Fred Alavi)**

Importance of Serotonin Receptor Selectivity

- Serotonin affects multiple central and peripheral biological functions in addition to modulating appetite

Behavioral effects:
Mood
Perception
Memory
Anger
Aggression
Fear
Stress responses
Appetite
Addiction
Sexuality

Other CNS effects:
Motor control
Cerebellar regulation
Sleep/circadian rhythms
CNS vascular tone
Emesis
Respiratory drive
Body temperature
Descending regulation of multiple organ systems

Central serotonergic drugs:
SSRIs
Tricyclic antidepressants
MAOIs
Other antidepressants
Buspirone
Atypical antipsychotics
Tryptans
5-HT₂ receptor antagonists (e.g. ondansetron)
Fenfluramine
Ergotamine/methysergide
Hallucinogens

- Complex regulation of heart rate
 - Regulates sinus node
 - Regulates AV node
- Can induce atrial fibrillation in high 5-HT states, e.g., carcinoid
- Involved in heart development
- Involved in valvulopathy
- Ventricular remodeling in CHF

- Regulates respiratory drive
- May be involved in SIDS
- Involved in pathogenesis of pulmonary hypertension

- Regulates gastric emptying
- Regulates intestinal peristalsis
- Regulates intestinal secretion
- Regulates colonic tone
- Regulates pancreatic secretion
- May regulate beta cells
- Nausea/emesis
- Involved in IBS
- Platelet-derived 5-HT involved in hepatic regeneration

- Pain and nociception
- Complex effects on HPA axis and stress responses
- Early embryonic development

Berger et al (2009) Annu Rev Med

Serotonin mediates its effects via 5HT Receptors (5HTRs)

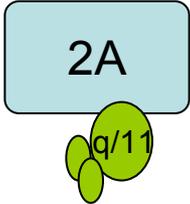
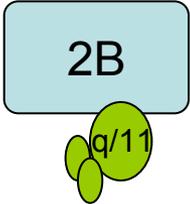
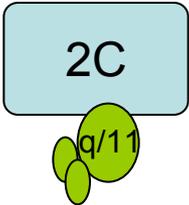
- Seven 5HTR families, categorized by sequence similarity and signaling mechanism
- Response to serotonergic drugs, in part, stems from profile of 5HTRs activated

Serotonin Receptor Families		
5HTR Family	No. Subtypes	Signal Transduction
5HT1	5	GPCR, ACi
5HT2	3	GPCR, Gq/11 PLCs
5HT3	5	Ion Channel
5HT4	1	GPCR, Gs, ACs
5HT5	2	GPCR, Gi/o, ACi
5HT6	1	GPCR, Gs, ACs
5HT7	1	GPCR, ACs

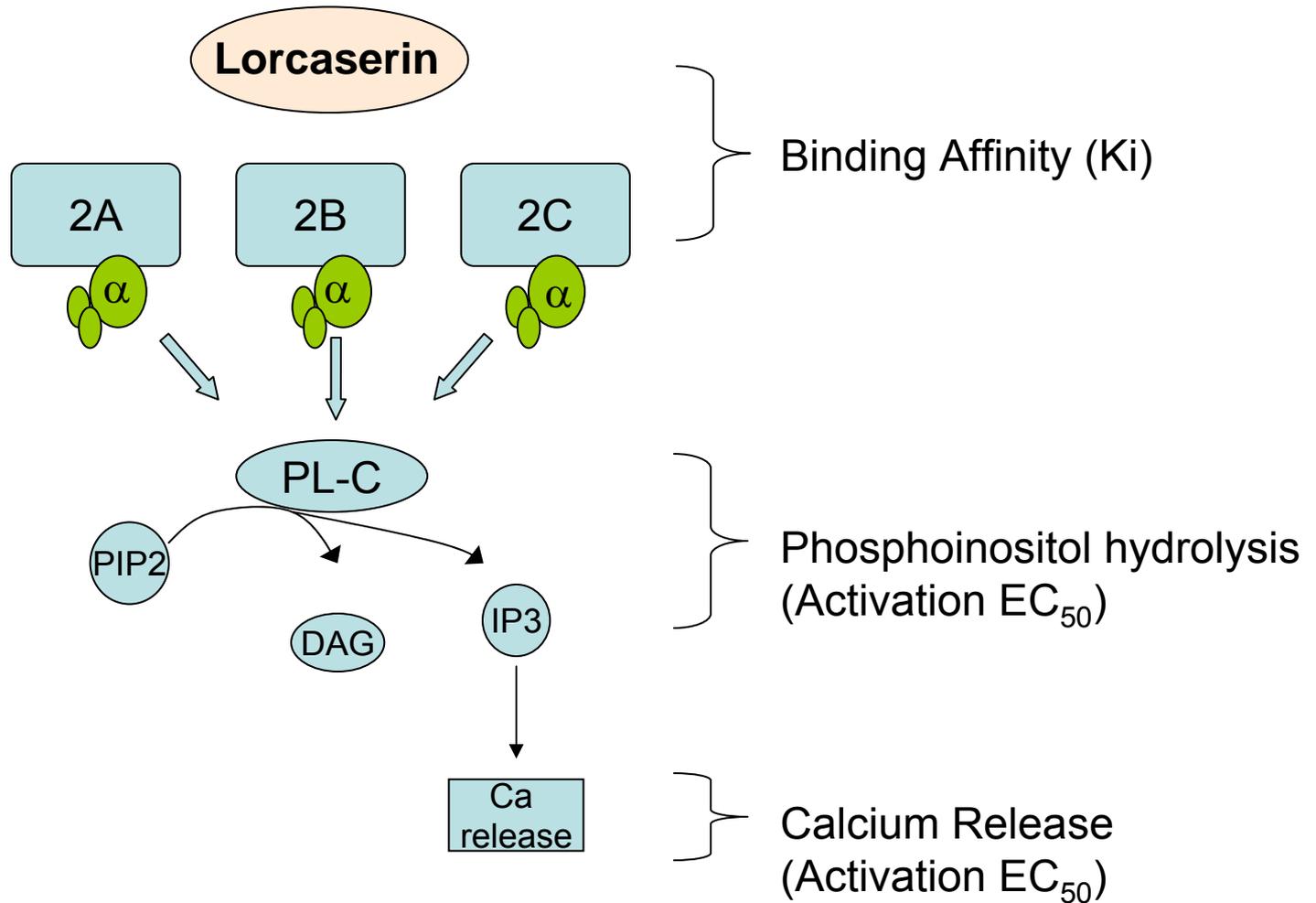
Lorcaserin targets 5HT2C subtype of 5HT2 family

5HTR SubType	Lorcaserin Receptor Binding, Ki (nM)
5HT2C	13
5HT1A	50 (Cerep) 724 (Arena) Activation EC50, 1400nM
5HT3	4400
5HT4c	19000
5HT5a	3700
5HT6	2000
5HT7	640

GPCR, G-protein coupled receptor
PLC, phospholipase C
ACs/i, adenylate cyclase stimulation/inhibition

5HT2 subtype	Distribution/Function	
	CNS	Periphery
	<p>Drug-induced hallucinogenic responses</p> <p>Anxiety, behavior, locomotion</p>	<p>Liver, renal mesangium mitogenesis Vasoactive (pulmonary/coronary vessels) Adipocyte differentiation, Platelet aggregation, enteric neurotransmitter</p>
	<p>Motor behavior, Anxiety, cerebrovascular tone</p>	<p>Drug-induced valvulopathy Pulmonary vascular remodeling/hypertension Hepatocellular mitogen</p>
	<p>Appetite suppression Locomotion, Anxiety DA output, stress response</p>	<p>Limited expression</p>

In vitro Assessment of Lorcaserin Selectivity for 5HT2 receptor subtypes



Lorcaserin: Binding and activation of 5HT2 receptor subtypes

	5HT2A	5HT2B	5HT2C
Receptor Binding (K _i , nM)	92	147	13
PI Hydrolysis (EC ₅₀ , nM)	14 to 133	82 to 811	1.9 to 9
Calcium release (EC ₅₀ , nM)	52	350	6

Fold 'Functional Selectivity' for 5HT2c versus 5HT2A/B (EC₅₀ for 2C / EC₅₀ for 2A or 2B)

	vs 5HT2A	vs 5HT2B
PI hydrolysis or Ca release	8x to 15x	45 to 90x

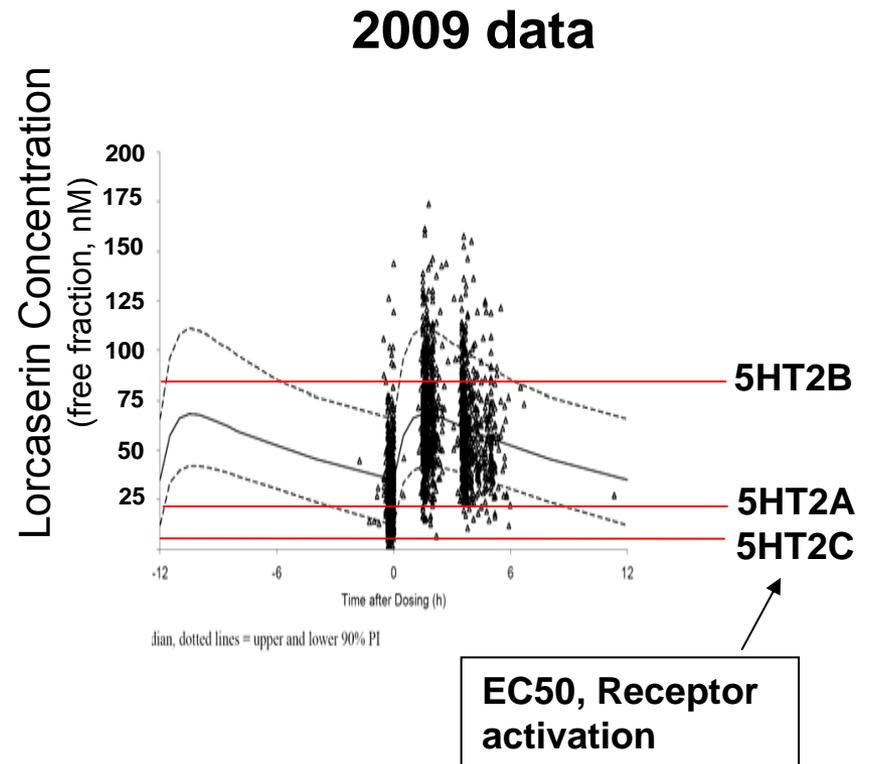
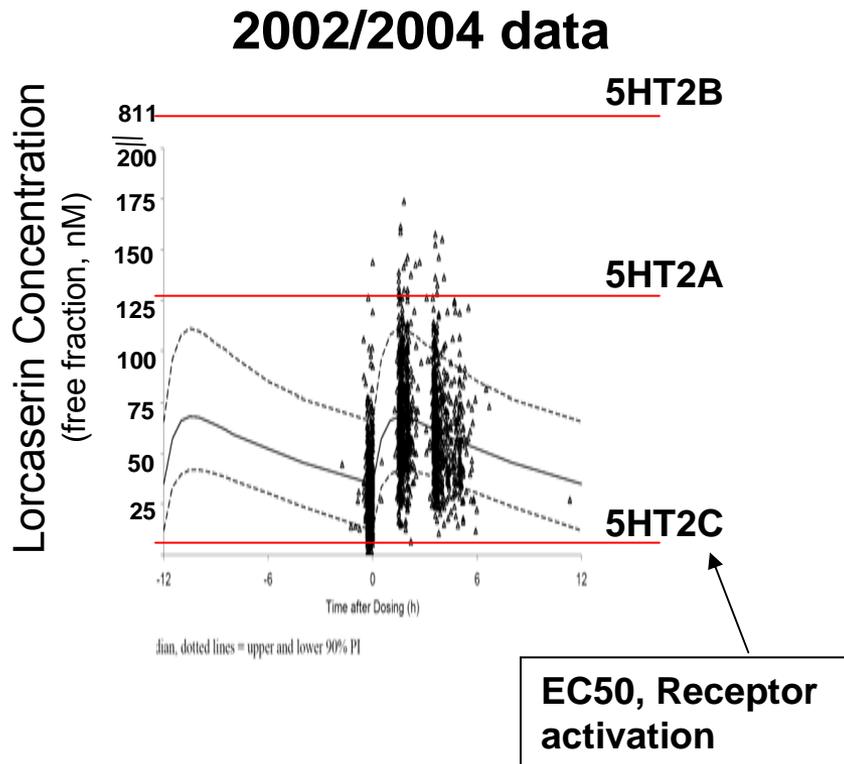
Lorcaserin: Variation in estimates of lorcaserin potency

- Functional selectivity advantageous provided clinical drug concentration falls within selective range *in vivo*
- Estimated potency of lorcaserin in vitro for 5HT2R varies by 10-fold across studies

PI Hydrolysis (EC50, nM)	5HT2A	5HT2B	5HT2C
2002/04 data	133	811	9
2009 data	14	82	1.9

- 5HT2A/B Receptor activation unlikely if lower potency, plausible if higher potency compared to free lorcaserin level of 53 ± 17 nM in plasma

Lorcaserin: Variation in estimates of lorcaserin potency vs. clinical exposure



Lorcaserin receptor selectivity: In vitro assessment

- Lorcaserin binds to and activates 5HT_{2C} with greater affinity and potency than for 5HT_{2A} and 2B
- Receptor selectivity of lorcaserin in different tissues *in vivo* is difficult to predict due to variable *in vitro* potency data
- Lorcaserin does not interact at relevant concentrations to 5HT/NA/DA transporters, exposure to active/non-active metabolites is limited

Lorcaserin receptor selectivity: Neurological toxicity in animals

Assessed by:

- Dedicated short-term behavioral studies (rats)
- Cage side observations in standard toxicology studies

5HT2 receptor activation data reasonably similar across species

Lorcaserin potency data for 5HT2 receptors (EC50, nM) (2009 data, PI hydrolysis)			
	5HT2 A	5HT2 B	5HT2 C
Human	14	82	1.8
Rat	31	21	5
Monkey	23	61	2

Lorcaserin receptor selectivity: Neurological toxicity in animals

- Lorcaserin induced behaviors reasonably attributable to known 5HT_{2C}-related effects
 - ↓ Activity, ↑ Resting time, delayed response to physical stimulus, penile grooming
- Lorcaserin did not provoke 5HT_{2A}-related behaviors as seen with DOI, a mixed 2A/2C agonist
 - Wet dog shakes, back fasciculation
- Lorcaserin did not release 5HT or DA from nucleus accumbens in rats by microdialysis probing, effects associated with drugs of abuse

Lorcaserin receptor selectivity: Neurological toxicity in animals

Lorcaserin did not elicit clear 5HT2A-related neurotoxicity at a dose that reduces food intake, supporting 5HT2C selectivity *in vivo*

Concerns with study design lessen confidence of animal neurological data

- Response to lorcaserin and DOI evaluated one year apart
- DOI (2A/2C agonist) did not elicit 2C behaviors
- Interpreting lack of DA release confounded by:
 - No positive control of DA release
 - 5HT2C reportedly inhibits DA release^{1,2}
 - Measuring basal DA release may have missed 5HT2A effect^{2,3}

Limitations preclude definitive conclusion regarding 2A-related behavior in animal studies with lorcaserin

¹Filip and Bader (2009) Pharm Reports

²Giorgetti and Tecott (2004) Eur J Pharmacol

³DiGiovanni et al (2000) Synapse

Lorcaserin receptor selectivity: Cardiac toxicity in animals

- Cardiac valves are enriched for expression of 5HT2B (human, rat, monkey)
- Drugs associated with clinical valvular heart disease display high potency for 5HT2B activation

Comparative potency for 5HT2B and 2C receptor activation (Inositol phosphate accumulation, EC ₅₀)			
Drug	5HT2 C	5HT2 B	Clinical exposure
(+) norfenfluramine*	13	18	110 nM (total) 44 nM (free%)
Pergolide*	--	53	1000 nM (total) 100 nM (free%)
Lorcaserin	2-9	82-811	178 nM (total) 53 nM (free%)

*Rothman et al (2000); Fitzgerald et al (2000)

Lorcaserin receptor selectivity: Cardiac toxicity in animals

Assessed by:

- Histological evaluation of cardiac tissue, including all valves and chordae tendineae (incidence/severity reported)
- Conducted in rats (≤ 24 months) and monkeys (≤ 12 months)
- Cross-species potency at 5HT2B receptor reasonably similar
- Plasma drug levels $\sim 20,000$ nM reached in studies

Lorcaserin: Cross-species potency for activation of 5HT2B receptors (EC50, nM)			
	2002/04 data	2009 data	Range of lorcaserin plasma levels achieved
Rat	226	21	150 to 20,000 nM
Monkey	--	61	400 to 20,000 nM
Human	811	82	178 \pm 58 nM

Lorcaserin receptor selectivity: Cardiac toxicity in animals

Results:

- Cardiac histology, including valve tissue, reported as within normal limits in all studies, rats and monkeys
- No evidence that lorcaserin induced fibrotic lesions of cardiac tissue in animals up to 100-times the clinical C_{max}, ~70-times clinical AUC
- Supports view that lorcaserin has greater selectivity for 5HT_{2C} in vivo than predicted by in vitro potency data

Lorcaserin receptor selectivity: Cardiac toxicity in animals

Limitations of models and studies lessen confidence in animal cardiac data

- No robust, reproducible animal model of drug-induced VHD
 - Positive reports: Pergolide, 5HT_{2C} selective agonist
 - Mixed reports: Serotonin, Fenfluramines
 - No reports of drug-induced VHD in non-human primates
- Toxicology studies did not include a ‘positive control’ for drug-induced valvulopathy
- Other drug-induced VHD-related endpoints reported in the literature were not included in the preclinical evaluation for lorcaserin (proliferative markers, echocardiography)

Limitations preclude definitive conclusion regarding valvulopathy in animal studies with lorcaserin

Summary: In vivo preclinical neurological and cardiac assessment

- Neurological and Cardiac assessments did not identify major toxicities considered related to 5HT_{2A/2B} activation in animal studies, supporting the view that lorcaserin has greater functional selectivity for 5HT_{2C} than predicted by *in vitro* studies
- Limitations in the neurological and cardiac assessments are sufficiently concerning to lessen confidence in this conclusion