Standards in Antidepressant Trials: Gepirone

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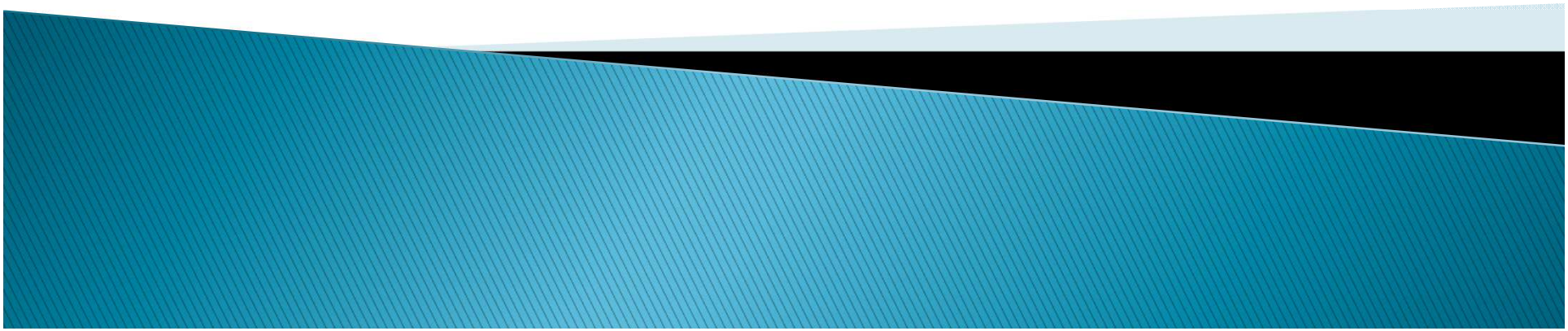
Before the FDA Psychopharmacologic Drugs Advisory Committee
December 1, 2015



Short Term Efficacy: Gepirone

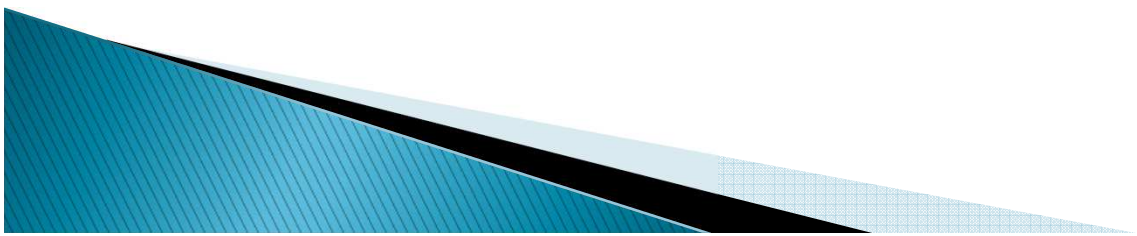
Trials with negative trends appear in red. Positive results appear in blue.

Gepirone: Phase 2/3 randomized placebo-controlled short-term efficacy trials for MDD (n=9)				
	Trial No*	Protocol-specified outcome measure	Treatment Effect (Gep - Pbo difference)	p-value
1	ORG 134004	HAMD-25	0.87	0.42
2	ORG 134017	MADRS	0.5	0.65
3	ORG 134023	HAMD-17	0.13	0.9
4	ORG 134006	HAMD-25	0.06	0.95
5	ORG 134002	HAMD-17	-0.71	0.42
6	FK-GBE-008	HAMD-17	-1.38	0.2
7	CN105-053	HAMD-17	-2.00	0.19
8	FK-GBE-007	HAMD-17	-2.45	0.018
9	ORG 134001	HAMD-17	-2.47	0.013
* Three trials, 052, 078, and 083, are not included because they were terminated early.				

Approved Antidepressants

Gepirone's sponsor has argued that several approved drugs also produced large numbers of failed trials in clinical testing, suggesting the FDA is being unfair by denying approval in this case

- Citalopram (CELEXA), 1998
- Duloxetine (CYMBALTA), 2004
- Desvenlafaxine (PRISTIQ), 2008
- Vilazodone (VIIBRYD), 2011



Citalopram (CELEXA), 1998

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Citalopram (CELEXA): Phase 2/3 randomized placebo-controlled short-term efficacy trials for MDD (n=5)*				
	Trial No	Measure	Treatment Effect (Cit - Pbo difference)	p-value
1	89306	MADRS	-0.09 to -1.99**	0.96 to 0.31**
2	89303	HAM-D	-0.59 to -2.75**	0.75 to 0.12**
3	91206	HAM-D	-0.63 to -2.91**	0.51 to < 0.01**
4	86141	HAM-D	-1.38	0.32
5	85A	HAM-D	-3.32	0.0344

* Two trials, 86A and 87A, were not included because they were terminated early.
** A range of values are presented for trials that included multiple dosing groups

Note: In addition to these five short-term trials, two positive long-term relapse-prevention trials helped form the basis of approval of CELEXA.

CYMBALTA and PRISTIQ

Positive results appear in blue.

Duloxetine (CYMBALTA): Phase 2/3 rand. pbo-controlled short-term efficacy trials for MDD (n=8)				
	Trial Number	Measure	Treatment Effect (Dul – Pbo difference)	p-value
1	HMAQb	HAMD-17	-0.04	0.96
2	HMATa	HAMD-17	-1.14 to -1.26*	0.222 to 0.138*
4	HMAYb	HAMD-17	-1.55 to 1.73*	0.54 to 0.25*
5	HMAQa	HAMD-17	-1.66	0.15
6	HMBHb	HAMD-17	-2.17	0.024
7	HMAYa	HAMD-17	-2.17 to -3.21*	0.007 to < 0.001*
8	HMATb	HAMD-17	-2.41 to -3.11*	0.022 to 0.003*
9	HMBHa	HAMD-17	-4.09	< 0.001

Desvenlafaxine (PRISTIQ): Phase 2/3 rand. pbo-controlled short-term efficacy trials for MDD (n=9)				
	Trial Number	Measure	Treatment Effect (Des – Pbo difference)	p-value
1	317	HAMD-17	-0.7	0.49
2	309	HAMD-17	-0.9	0.38
3	332	HAMD	-1.47 to -1.97*	0.065 to 0.018*
4	320	HAMD-17	-1.6	0.08
5	306	HAMD-17	-1.9 to -2.8*	0.076 to 0.002*
6	333	HAMD	-2.5 to -3.0*	0.002 to <0.001*
7	308	HAMD-17	-4.2 to -5.4*	0.008 to 0.002*
8	304	HAMD-17	not published	0.28
9	223	HAMD-17	not published	0.52 to 0.59*

*A range of values are presented for trials that included multiple dosing groups

Vilazodone (VIIBRYD), 2011

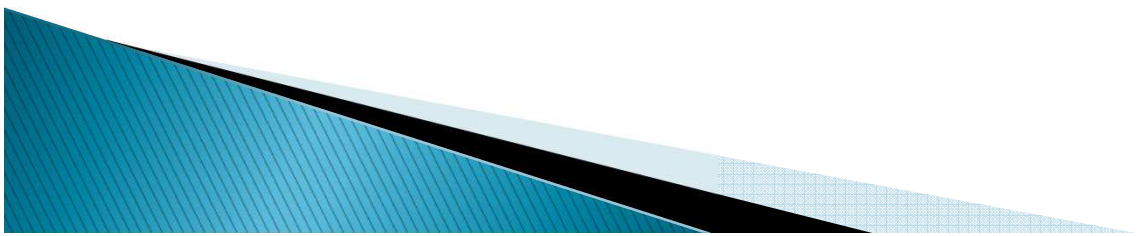
Trials with negative trends appear in red. Positive results appear in blue.

	Vilazodone (VIIBRYD): Phase 2/3 randomized placebo-controlled short-term efficacy trials of in MDD (n=7)			
	Trial Number	Measure	Treatment Effect (Vil- Pbo difference)	p-value
1	248	HAMD	0.5 to -1.2*	0.18 to 0.80*
2	244	HAMD	0.76	0.49
3	246	HAMD	-0.5 to -0.8*	0.41 to 0.58*
4	247	HAMD	-1.0	0.27
5	245	HAMD	1.6 to -0.3*	0.13 to 0.75*
6	CLDA-07-DP-02	MADRS	-2.5	0.009
7	GNSC-04-DP-02	MADRS	-3.2	0.001

* A range of values are presented for trials that included multiple dosing groups

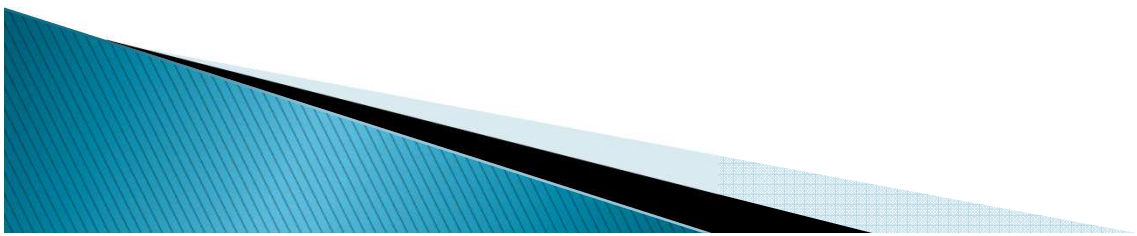
Failed/negative relapse-prevention trial

- Gepirone long-term relapse prevention trial failed to achieve a significant result.
- Such failure has occurred in only one out of 12 approved antidepressants.
- In the case of the one prior failed relapse-prevention trial, levomilnacipran (FETZIMA), approval was supported by four adequate, well-controlled positive short-term efficacy studies



Active-controlled trials

- FDA statisticians have pointed out that among the four trials of gepirone that included an active-controlled arm, active controls performed consistently better than gepirone ER or placebo.
- These trends remain troubling even acknowledging they did not reach statistical significance using the pre-planned analysis



Summary: Multiple Failures

- Unusually large number of failed/negative trials
- Trends in the wrong direction (drug worse than placebo) in 4 trials
- Failed relapse prevention trial
- Consistent trend of active controls performing consistently better than placebo

Each of these findings is rare among FDA-approved antidepressants. They have never occurred together.