

TRAVIVO® [Gepirone Extended Release (ER)]

Fabre-Kramer Pharmaceuticals

Presentation to the
Psychopharmacologic Drugs Advisory Committee

December 1, 2015

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Introduction

Daniel Burch, MD

Vice President & Global Head, Neuroscience

PPD

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Difficulties in Antidepressant Development – Failed Trials

~50% of trials with all approved antidepressants fail

- Placebo Response and Variability
- Disease Severity Thresholds
- Endpoint Management
- Adherence/Retention

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Contemporaneous Antidepressant Development Programs

Drug Name	Positive	Negative	Failed	Positive (%)
vilazodone	2	2	3	29
duloxetine	3	2	5	30
desvenlafaxine	3	5	1	33
citalopram	2	3	5	20

Source: FDA Summary Bases of Approvals for vilazodone, duloxetine, desvenlafaxine, citalopram;
www.accessdata.fda.gov/

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Why Are We Here?

- #1 cause of worldwide disability in developed countries (WHO, 2004)¹
- Treatment for MDD is empiric and often inadequate
 - Switching is common (2.65 average therapies prior 18 months)²
 - Additional options are needed; only 1/3 remit on their first antidepressant³
- Safety and tolerability profiles of current options limit acceptance and adherence

¹World Health Organization, Part 4: Burden of disease: DALYs, page 44

²Quelen C. et al 2014

³Rush, 2006

Why Are We Here?

- Approvability of gepirone ER for major depressive disorder (MDD) in adults
 - Substantial evidence of effectiveness for MDD
 - No claims sought for long-term treatment, pediatrics or sexual dysfunction
- Proposed dose: 60-80 mg

Why Are We Here?

- Request for Dispute Resolution
- Areas of agreement
 - Safety in keeping with general antidepressant
 - Trials 001 and 007 are adequate, well-controlled and robustly positive independent trials
- Areas for discussion
 - Magnitude of treatment effect
 - Interpretation of the remaining 10 trials

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Gepirone ER Characteristics

- Azapirone analogue
 - the 3'-OH metabolite is an active species
- Selective 5HT_{1A} receptor partial agonist
 - Does not affect 5-HT_{2A} or other serotonin receptors associated with adverse events
 - Not an SSRI or SNRI
- Gepirone ER is an extended-release formulation

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Regulatory History

Clinical Phase III Development of Gepirone ER

Early Studies; terminated early (BMS)	Studies performed in response to FDA advice (Organon and Fabre-Kramer)	Studies performed for other reasons* (Organon)
CN105-052	134001	
CN105-053	134002	134004
CN105-078	FKGBE007	134006
CN105-083	FKGBE008	134017
	134023	

*Maintenance study (28709) also performed

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Replicate Trials – Population / Endpoint / Conduct

Study	Design	Control(s)	Endpoint	Patient #
CN105-078	2-arm	pbo	HAMD-17	135
CN105-083	2-arm	pbo	HAMD-17	112
CN105-052	3-arm	pbo, fluoxetine	HAMD-17	108
CN105-053	3-arm	pbo, imipramine	HAMD-17	166
134001	2-arm	pbo	HAMD-17	202
134002	2-arm	pbo	HAMD-17	205
134023	2-arm	pbo	HAMD-17	246
FKGBE007	2-arm	pbo	HAMD-17	238
FKGBE008	2-arm	pbo	HAMD-17	195
134004	3-arm	pbo, fluoxetine	HAMD-25	391
134006	3-arm	pbo, paroxetine	HAMD-25	422
134017	3-arm	pbo, fluoxetine	MADRS	480

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3-Arm Comparator Trials for Approved Antidepressants

Investigational Drug	Year Approved	Short term 3-arm Comparator Studies	Positive**	Failed*	Negative**	Percentage Failed or Negative (%)
citalopram	1998	5	0	5	0	5/5 (100)
escitalopram	2002	2	1	1	0	1/2 (50)
duloxetine	2004	6	1	5	0	1/6 (83)
desvenlafaxine	2008	2	0	1	1	2/2 (100)
vilazodone	2011	3	0	3	0	3/3 (100)
TOTALS		18	2	15	1	16/18 (89)

*on primary efficacy endpoint

**on primary efficacy endpoint with assay sensitivity

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Gepirone ER Meets the Standard of Effectiveness in MDD

Trial	Primary Endpoint	Secondary Endpoints
134001	<i>Met primary endpoint</i>	<i>Met secondary endpoints</i>
134002	Directional trend	Directional trends
<i>FKGBE007</i>	<i>Met primary endpoint</i>	<i>Met secondary endpoints</i>
FKGBE008	Directional trend	Directional trends
134023	Did not meet endpoint	Did not meet endpoints
Meta-analysis	Favorable	Favorable on responder variable

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Gepirone ER is Effective in the Treatment of MDD

- MDD is a significant public health problem
- Totality of evidence (meta-analysis) of interpretable studies supports finding of substantial evidence of effectiveness
- Different mechanism of action
- Two positive, adequate and well-controlled trials, meeting the standard for regulatory approval
- Safe and well-tolerated in adult patients with MDD

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Agenda

Introduction	Daniel Burch, MD Vice President & Global Head, Neuroscience <i>PPD</i>
Rationale for Gepirone Development	Michael E. Thase, MD Professor of Psychiatry <i>Perelman School of Medicine, University of Pennsylvania</i>
Totality of Evidence for Effectiveness	Gary Koch, PhD Professor and Director, Biometric Consulting Laboratory <i>The University of North Carolina at Chapel Hill</i>
Gepirone Clinical Experience	Stephen Stahl MD, PhD Professor of Psychiatry <i>University of California, San Diego</i> Honorary Fellow <i>University of Cambridge</i>
Conclusions	Daniel Burch, MD Vice President & Global Head, Neuroscience <i>PPD</i>

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Additional Consultants

- Anita H Clayton, MD
 - Professor and Chairman, Psychiatry and Neurobehavioral Sciences, University of Virginia School of Medicine
- Leonard Derogatis, PhD
 - Professor of Psychiatry and Director, Maryland Center of Sexual Health, Johns Hopkins University School of Medicine
- Mary Johnson, PhD
 - Principal, MJ Biostat
- Lee-Jen (L.J.) Wei, PhD
 - Professor of Biostatistics, Harvard University School of Public Health

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Rationale for Gepirone Development

Michael E. Thase MD

Professor of Psychiatry
*Perelman School of Medicine, University of
Pennsylvania*

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MDD is a Significant Public Health Problem

- MDD is common, has an early onset and high rates of recurrence and chronicity
- In 2010, direct healthcare costs estimated at \$95+ billion
- The leading cause of disability and absenteeism in US
- Underlying cause in >60% of suicide (12th leading cause of death across age groups)

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2010 APA Practice Guideline: Selection of an Antidepressant

- Generally similar efficacy
- Antidepressants
 - First line – SSRIs, SNRIs, mirtazapine, or bupropion
 - Second line – TCAs, MAOIs (first-generation), other newer Rx
- Antidepressant choice depends on:
 - Side effects and safety issues
 - History of response or lack of response (MoA)
 - Drug interactions
 - Indication for comorbid disorder
 - Cost
 - Patient preference

APA = American Psychiatric Association
 MAOI = Monoamine oxidase inhibitor
 SNRI = Serotonin norepinephrine reuptake inhibitor
 SSRI = Selective serotonin reuptake inhibitor
 TCA = Tricyclic antidepressant

APA. *Am J Psychiatry*. 2010.
<http://psychiatryonline.org/content.aspx?bookID=28§ionID=1667485#654274>

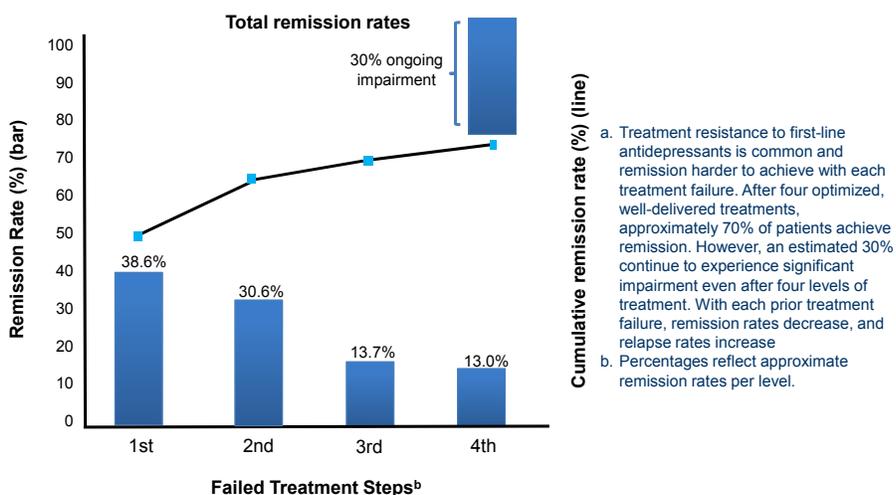
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Antidepressant Therapy: Unmet Needs

- Limited efficacy (~10-20% advantage in remission rates vs PBO in RCTs)
- Intolerable side effects for 10%
- Inconsistent effects on key symptoms (insomnia, anxiety)
- Relatively slow onset of action
- Better alternatives for nonresponders to first- and second-line medications

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STAR*D Treatment Outcomes Across Four Sequential Antidepressant Trials^a



Greden. Am J Psychiatry. 2013;170:578-581
 Greden et al. Treatment resistant depression: overview of the University of Michigan Depression Center Roadmap, in Treatment Resistant Depression: A Roadmap for Effective Care. Edited by Greden et al., Washington, DC, American Psychiatric Publishing, 2011

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Recently Introduced Antidepressants: A Decade of Modest Advances

- 2006: Selegiline TDS (MAOI)
- 2007: Desvenlafaxine (SNRI)
- 2011: Vilazodone (SRI & 5-HT_{1a} partial agonist)
- 2013: Vortioxetine (SRI with multiple 5-HT receptor actions)
- 2013: Levomilnacipran (SNRI)

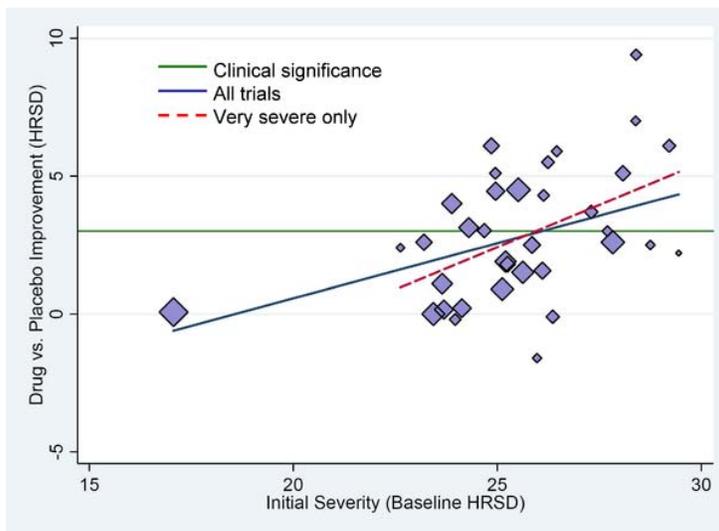
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Signal Detection in Antidepressant RCTs: The State of the Problem

- At least 50% of contemporary RCTs fail to detect statistically significant effects (i.e., drug > placebo) on the primary outcome measure
- The primary reason for the high failure rate is a large, progressively growing PBO response rate
- Difficult to differentiate known ADs from PBO when PBO response rate is >40%
- Difficult to differentiate known ADs from PBO in samples with milder depressions

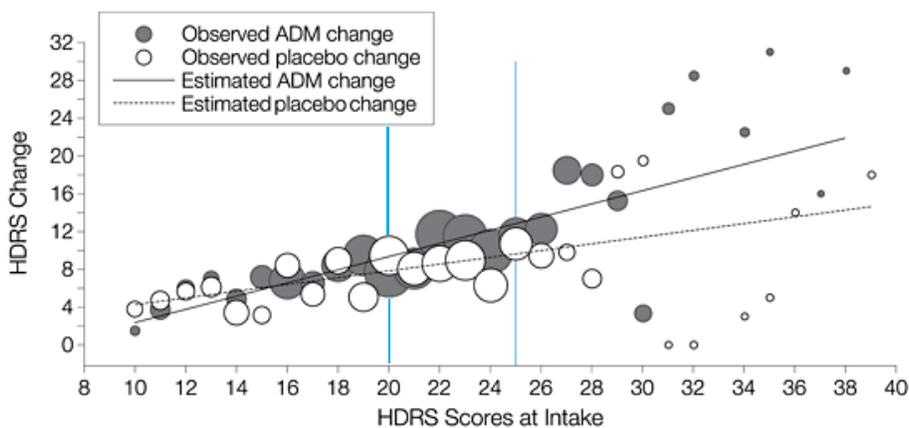
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Kirsch et al. Meta-analysis of FDA Submission Data



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JAMA Meta-analysis: Pre-treatment Severity and Response to Antidepressant and Placebo



Fournier, J. C. et al. JAMA 2010;303:47-53.

JAMA 24

Sexual Dysfunction Contributes to the Morbidity of Depression

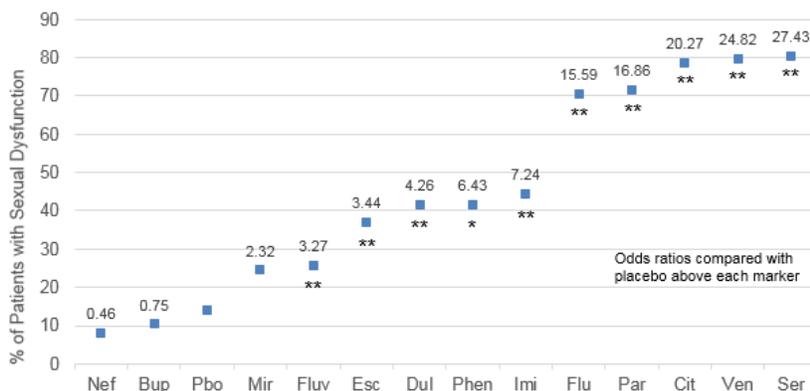
- 3/4 of depressed patients have sexual dysfunction prior to antidepressant treatment
- Sexual dysfunction in depression affects quality of life, as well as reproductive ability in young adults
- Patients with a combination of depression and sexual dysfunction are more prone to suicide
- Antidepressants with SSRI or SNRI mechanisms further interfere with sexual function
- 90% of patients who develop treatment emergent sexual dysfunction will stop their medication, exacerbating the problem

Nurnberg & Hensley, 2003
Clayton, 2006

Harsh, 2008
Higgins, 2010

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Current antidepressants exacerbate sexual dysfunction



Bup, bupropion; Cit, citalopram; Dul, duloxetine; Esc, escitalopram; Flu, fluoxetine; Flu, fluvoxamine; Imi, imipramine; Mir, mirtazapine; Nef, nefazodone; Par, paroxetine; Pbo, placebo; Phen, phenelzine; Ser, sertraline; Ven, venlafaxine

*p-value =0.01

**p-value <0.00001

Serretti & Chiesa, 2009

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Additional Treatment Options Are Needed

- MDD is a serious illness that seriously impacts patients and society: it is one of the greatest public health problems
- Many patients need to try multiple antidepressants before achieving remission
- Currently approved antidepressants have sexual side effects, resulting in poor adherence and reduced quality of life

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Totality of Evidence for Effectiveness

Gary G. Koch PhD, Professor
Department of Biostatistics
The University of North Carolina at Chapel Hill

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Objectives

- Review studies 134001 and FKGBE007
 - Two adequate and well-controlled studies that demonstrated efficacy (met primary endpoints; robust with respect to secondary endpoints)
- Meta-analysis as a tool to identify the extent to which efficacy from two positive studies is still demonstrated after dilution via integration with 3 additional studies most comparable to them
- Sensitivity assessment for efficacy results via meta-analysis with more extensive dilution through inclusion of additional and less comparable studies

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STUDIES 134001 & FKGBE007: Mean Change from Baseline in Primary and Secondary Efficacy Variables at Endpoint Week 8 (ITT/LOCF)

Parameter	134001				FKGBE-007			
	Gep-ER N=101	Placebo N=103	Δ	P-value	Gep-ER N=116	Placebo N=122	Δ	P-value
HAMD-17	-9.04	-6.75	-2.29	0.018	-10.22	-7.96	-2.26	0.032
HAMD-21	-10.01	-7.49	-2.51	0.021	-11.07	-8.79	-2.28	0.043
HAMD-25	-11.57	-8.19	-3.38	0.007	-12.65	-9.85	-2.80	0.029
HAMD-28	-13.27	-9.60	-3.68	0.013	-15.04	-11.83	-3.21	0.032
MADRS	-12.28	-9.22	-3.06	0.023	-13.72	-9.94	-3.78	0.008
HAMD Item 1	-1.16	-0.78	-0.39	0.005	-1.22	-0.97	-0.32	0.101
CGI Severity	-1.19	-0.79	-0.39	0.016	-1.30	-0.92	-0.38	0.015

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Studies 134001 & FKGBE-007: Responder Rates (pre-specified)

Parameter	134001				FKGBE-007			
	Gep-ER	Pbo	Δ	P-value	Gep-ER	Pbo	Δ	P-value
HAMD-17 Responders	43.6%	30.7%	12.9%	0.059	45.7%	29.5%	16.2%	0.014
HAMD-17 Remitters	28.7%	14.9%	13.8%	0.017	34.5%	20.5%	14%	0.019
HAMD-25 Responders	45.5%	28.7%	16.8%	0.014	48.3%	30.3%	18.0%	0.007
CGI Responders	43.6%	35.6%	7.92	0.251	48.3%	34.7%	13.6%	0.045

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Role of Meta-Analysis for Sensitivity Assessments for Efficacy Results

- Evaluate homogeneity and strength of evidence as we broaden the criteria for study inclusion
 - Begin with strict criteria to identify “interpretable” studies for integrating through exclusion of less comparable studies
- Treatment effect is expected to be diluted as less comparable studies are additionally included, and the integration becomes more heterogeneous
- Reasonable preservation of overall strength of evidence well supports efficacy results from studies 134001 and FKGBE007 not being due to chance regardless of their dilution via their heterogeneous integration with less comparable studies

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Criteria for Classifying an Individual Study as Interpretable for Efficacy

- Adequate and well-controlled trial
 - Completed in accordance with protocol
- Appropriate study population
 - Major Depressive Disorder
- Sufficient severity of illness
 - Minimum HAMD-17 score required at entry or substantial majority of patients with baseline HAMD-17 \geq 20
- Sufficient dosing
 - Doses titrated to therapeutic range
- Assay sensitivity (if active control present)
 - Clearly significant differences between active control and placebo for primary endpoint and many secondary endpoints

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Criteria for Classifying an Individual Study as Uninterpretable for Efficacy

- Premature termination
 - Low power and incomplete data
- Insufficient dosing
 - Low dose groups included in study
- Insufficient baseline severity
 - No minimum HAMD-17 score required at entry or many patients with baseline HAMD-17 $<$ 20
- Lack of assay sensitivity
 - Absence of clearly significant differences between active control and placebo for primary endpoint and many secondary endpoints
- FDA agrees study is uninformative for evaluation of efficacy (per FDA Briefing Document)

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Interpretable vs. Uninterpretable

- Interpretable studies are more suitable for a more interpretable sensitivity oriented meta-analysis
 - Adequate, well-controlled, homogeneous with respect to key design features (e.g., design, population, dose, duration), regardless of outcome
 - Positive: Statistically significant treatment effect for the primary efficacy variable based on the pre-specified analysis plan
 - Demonstrates assay sensitivity (if active control arm is included)
 - Negative: Investigational drug is not significantly different from placebo
- Uninterpretable or “failed” studies can have inclusion in a pessimistic sensitivity meta-analysis for which heterogeneity can adversely influence interpretation
 - Deficiencies in design or conduct
 - Lack of assay sensitivity

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Criteria for Exclusion of Studies

Study # (Chronological Order)	Prematurely terminated	Insufficient Dosing	Insufficient Baseline Severity	Lack of Assay Sensitivity	FDA Agreement Uninformative for Efficacy
CN105-078	X	X			X
CN105-083	X	X			X
CN105-052	X	?		X	X
CN105-053	X	?		?	
134001					
134002					
134004			X	X	
134006			X	X	
FKGBE007					
FKGBE008					
134017				X	
134023					

“X” denotes that a criterion for exclusion applied

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Seven Trials Were Uninterpretable – Confounding Issues

Study (Chron. Order)	Power	Baseline HAMD-17	Mean Dose	% Dropout		Assay Sens.	% Placebo Response	
				Gep-ER	Placebo		HAMD	CGI
CN105-078 +	62%	22.3	40.5	42.1	30.6	N/A	28.4	38.3
CN105-083 +	53%	23.9	43.9	38.1	34.1	N/A	37.1	43.6
CN105-052	43%	25.2	43.4	38.9	50.0	No	41.7	56.8
CN105-053	63%	23.9	46.4	41.4	60.7	?	44.8	56.3
134001 *	80%	22.7	61.1	27.5	23.6	N/A	29.7	35.6
134002 *	80%	24.0	57.9	31.8	28.7	N/A	38.5	44.7
134004	80%	19.6	67.1	36.3	21.3	No	38.8	42.3
134006	85%	19.0	55.3	31.3	24.3	No	42.0	46.9
FKGBE007 *	85%	23.9	58.2	21.8	17.8	N/A	32.9	34.7
FKGBE008 *	85%	24.2	60.0	24.0	21.5	N/A	34.9	37.8
134017	85%	23.3	58.9	31.5	21.3	No	46.6	52.8
134023 *	85%	22.9	61.3	26.0	21.3	N/A	35.1	39.0

* Interpretable study

+ Study was only 6 weeks duration, compared to 8-9 weeks for other studies

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Summary of Two-Armed Studies (Gepirone ER vs. Placebo)

Study	Change in HAMD-17	p-value	Summary
134001	-2.29	0.018	Significant treatment effects for primary and secondary efficacy variables (p<0.05)
FKGBE007	-2.26	0.032	Significant treatment effects for primary and secondary efficacy variables (p<0.05)
134002	-0.67	0.446	Positive trends for all variables
FKGBE008	-1.5	0.159	Positive trends for all vars; p<0.05 for HAMD-17 (Wks 2, 3, 6) and MADRS (Wks 2, 3, 4, 6)
134023	0.0	0.947	No trends or significance for any variables
CN105-078	-0.9	0.451	Terminated early, 62% power; positive trends for high dose; 6 wks only
CN105-083	-0.5	0.742	Terminated early, 53% power; positive trends for high dose; 6 wks only

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Summary of Three-Armed Studies (Gepirone ER vs. Active vs. Placebo)

Study	Active Control, Endpoint	Change in endpoint; p-value	Summary
		Active vs. PBO	
CN105-052	fluoxetine, HAMD-17	-0.5; <i>p=0.798</i>	Terminated early, 43% power; comparator failed on primary endpoint
CN105-053	imipramine, HAMD-17	-2.5; <i>p=0.144</i>	Terminated early, 63% power; only 1 site (of 2) completed enrollment; comparator failed on primary endpoint
134004	fluoxetine, HAMD-25	-1.03; <i>p=0.325</i>	MDD-AF; comparator failed on primary endpoint; high placebo response (42%)
134006	paroxetine, HAMD-25	-1.58; <i>p=0.178</i>	MDD-AF, comparator failed on primary endpoint; high placebo response (46%)
134017	fluoxetine, MADRS	-1.15; <i>p=0.299</i>	Comparator failed on primary endpoint; high placebo response (53%)

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Summary of the 5 Interpretable Clinical Studies

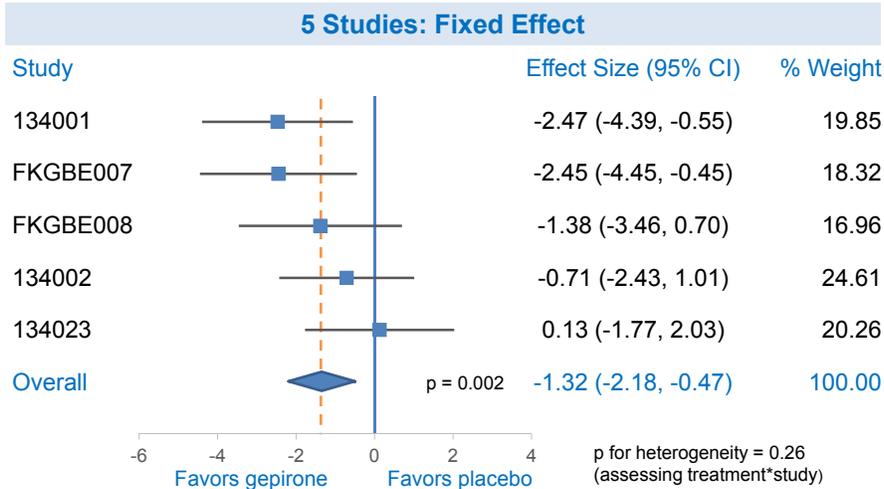
Study	# of Subjects (ITT)		HAMD-17 Difference; p-value	
	Gep ER	PBO	Baseline-adjusted*	Protocol defined analysis**
134001	101	101	-2.47; <i>p=0.013</i>	-2.29; <i>p=0.018</i>
FKGBE007	116	122	-2.45; <i>p=0.018</i>	-2.26; <i>p=0.032</i>
FKGBE008	96	99	-1.38; <i>p=0.195</i>	-1.5; <i>p=0.159</i>
134002	102	103	-0.71; <i>p=0.417</i>	-1.5; <i>p=0.159</i>
134023	123	123	0.13; <i>p=0.898</i>	0.0; <i>p=0.947</i>

* Difference (Gep ER – PBO) based on adjusted mean change from baseline (ANCOVA w/fixed effects for treatment, center, baseline as covariate).

** Difference between LS means (ANOVA w/fixed effects for treatment and center).

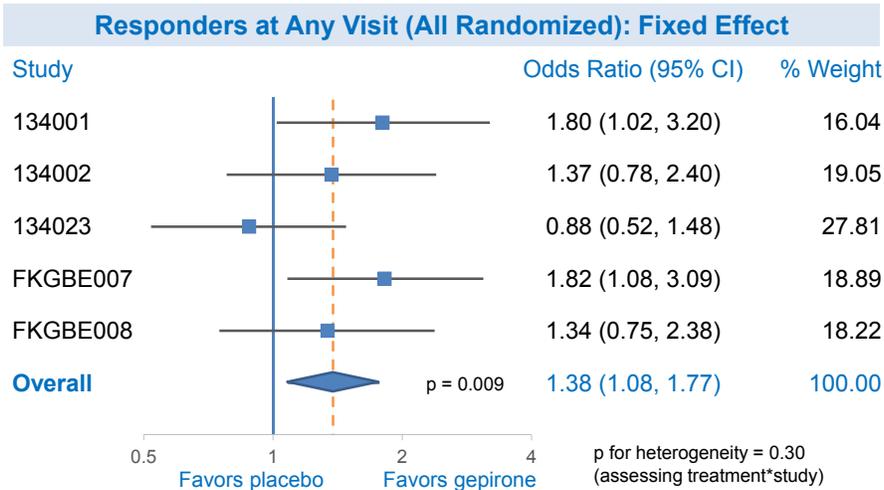
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Meta-Analysis of Mean Change in HAMD-17: 5 Interpretable Studies



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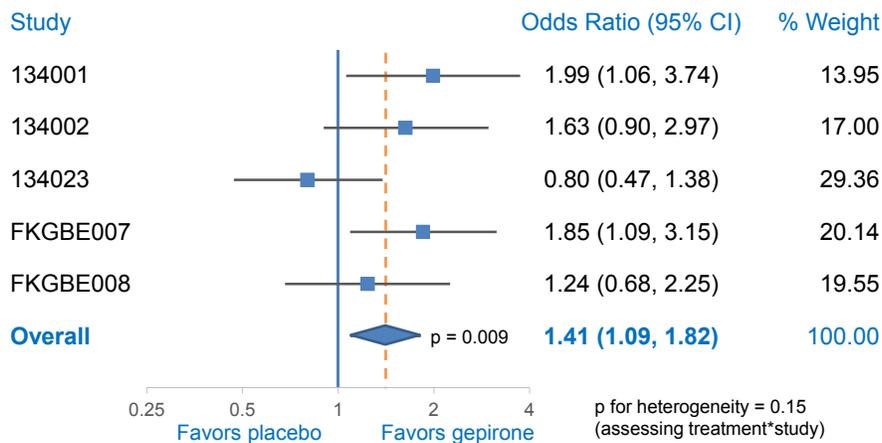
HAMD-17 Responder Analysis (Pre-Specified)



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HAMD-17 Responder Analysis (Sensitivity)

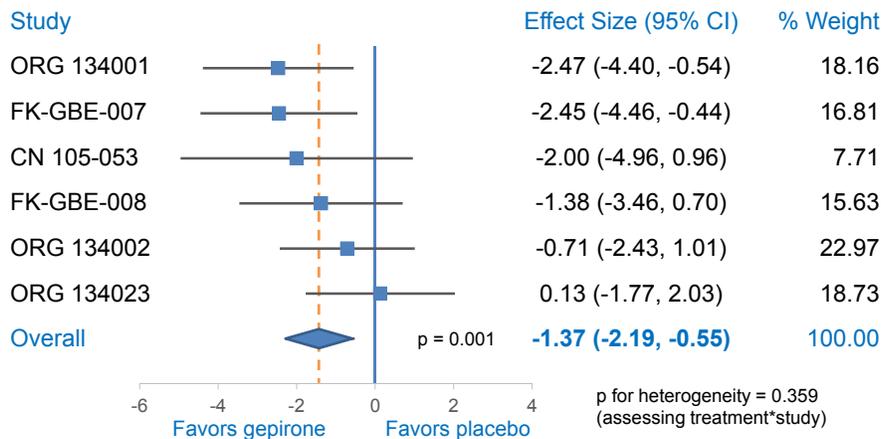
Responders at Final Visit (All Randomized): Fixed Effect



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Mean Change in HAMD-17: 6 Studies (including CN105-053)

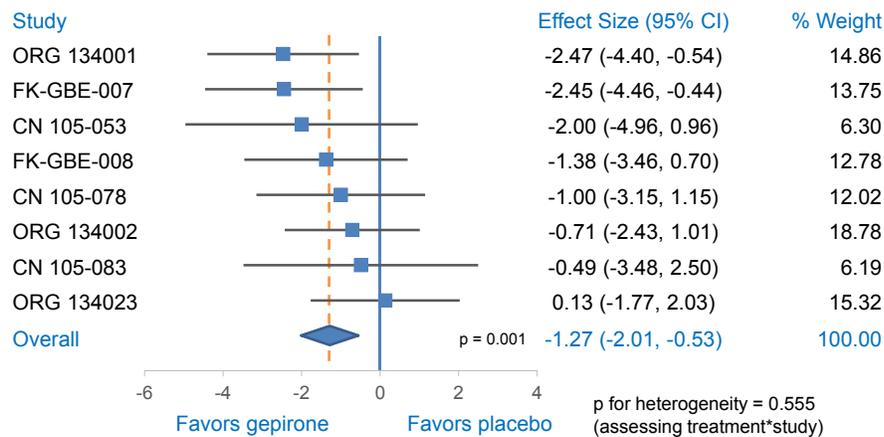
6 Studies: Fixed Effect



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Mean Change in HAMD-17 Using Fixed Effect Model: 8 Studies (5 int. + 053, 078 & 083)

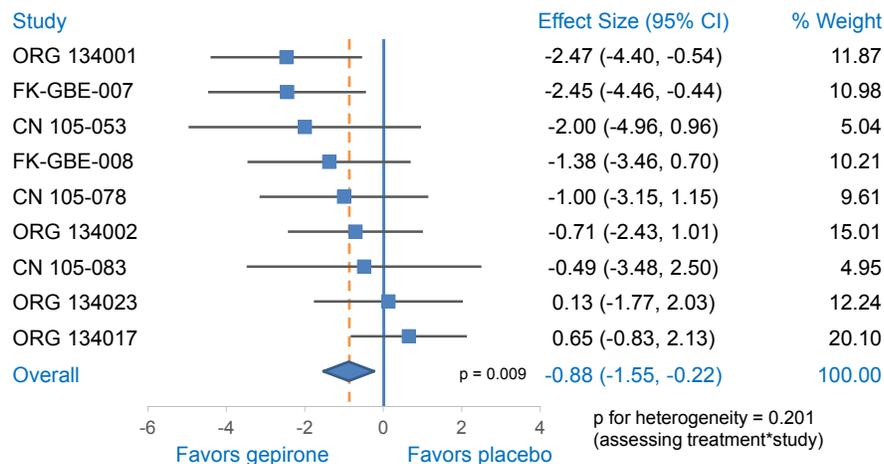
8 studies (5 interpretable + 053, 078 & 083): Fixed Effect



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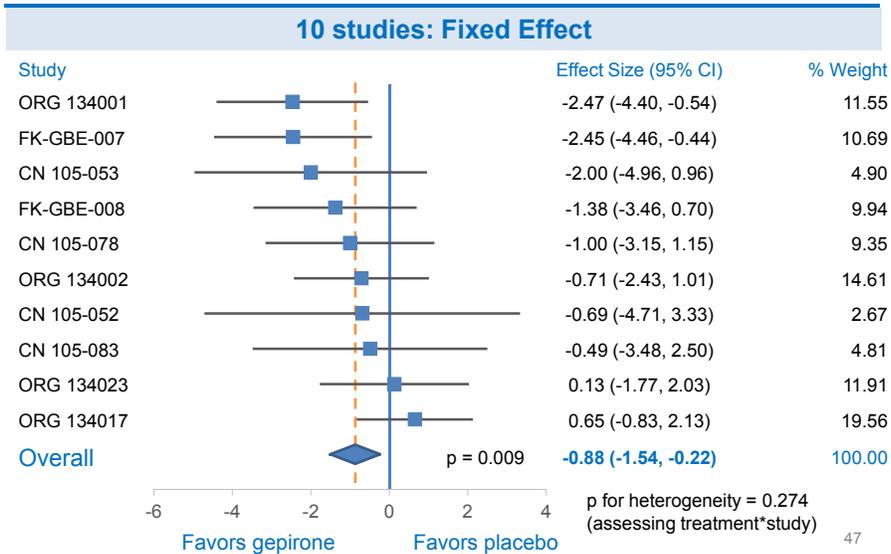
Mean Change in HAMD-17 Using Fixed Effect Model: 9 Studies (5 int. + 017, 053, 078 & 083)

9 studies (5 interpretable + 017, 053, 078 & 083): Fixed Effect

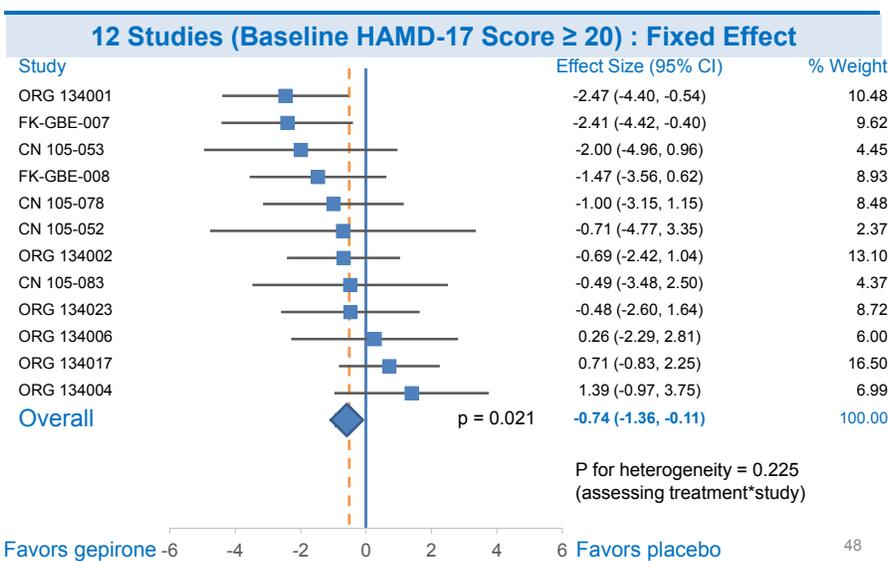


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Mean Change in HAMD-17: 10 Studies (All except 134004 & 134006)



Mean Change in HAMD-17: All 12 Studies (Subjects w/Baseline HAMD-17 ≥ 20)



Fisher's Method for Combining P-values Gepirone vs. Placebo: HAMD-17 Change from Baseline

Study	Core	Core +053	Core + 053 + 078 + 083	Core + 053 + 078 + 083 + 017	All 12 Studies	All 12 Studies (HAMD-17 ≥ 20)
134001	0.00646	0.00646	0.00646	0.00646	0.00646	0.00646
FKGBE007	0.00884	0.00884	0.00884	0.00884	0.00884	0.00992
134002	0.2087	0.2087	0.2087	0.2087	0.2087	0.2179
FKGBE008	0.09735	0.09735	0.09735	0.09735	0.09735	0.08515
134023	0.5512	0.5512	0.5512	0.5512	0.5512	0.328
CN105-052					0.3685	0.3655
CN105-053		0.0945	0.0945	0.0945	0.0945	0.0945
CN105-078			0.181	0.181	0.181	0.181
CN105-083			0.37345	0.37345	0.37345	0.37345
134004					0.9085	0.875
134006					0.635	0.5795
134017				0.804	0.804	0.8175
# Studies	5	6	8	9	12	12
Combined P-value	0.0015	0.0009	0.0012	0.0017	0.0124	0.0090

Individual study p-values are from ANCOVA model applied to change from baseline HAMD-17 at endpoint (ITT/LOCF), with Treatment and Center as fixed effects, baseline HAMD-17 as covariate.

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Conclusions Regarding the Efficacy of Gepirone ER-Based on Sensitivity Oriented Meta-Analyses

- Meta-analyses of the primary efficacy parameter and responder rates for the five interpretable studies were clearly statistically significant in favor of gepirone ER
- The effect for responder rates was maintained when all drop-outs were considered as non-responders for the five interpretable studies, a more pessimistic assumption than that used in the original studies
- Meta-analyses for the five interpretable studies also show a clinically meaningful effect size for responder rate for gepirone ER
- The scope of more inclusive sensitivity meta-analyses provide complementary support for the findings from the individual interpretable studies that gepirone ER is effective in the treatment of MDD

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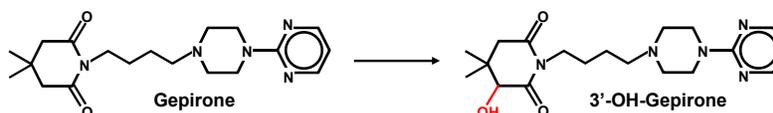
Gepirone Clinical Experience – Mechanism of Action

Stephen Stahl MD, PhD
 Professor of Psychiatry
 University of California, San Diego
 Honorary Fellow
 University of Cambridge

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Gepirone Overview

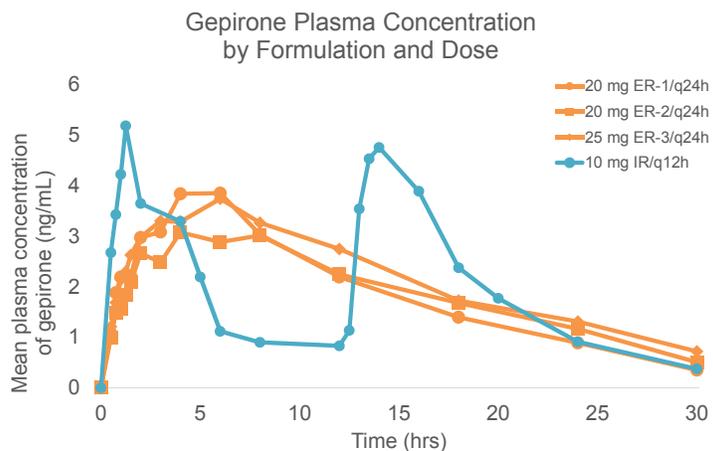
- Gepirone is an azapirone, and the 3'-OH metabolite is an active species



- The 3'-OH metabolite acts specifically and uniquely at the 5HT_{1A} receptor
 - Does not affect 5-HT_{2A} or other serotonin receptors associated with adverse events
- Gepirone ER was formulated to reduce C_{max} without impacting AUC₃₀

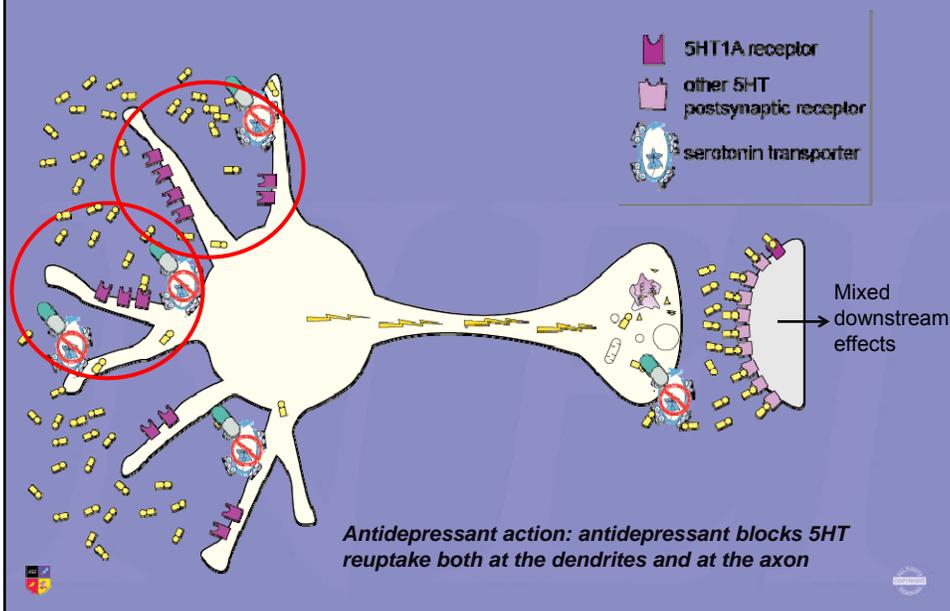
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Gepirone ER Pharmacokinetic Characteristics



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Mechanism of Action of SSRIs

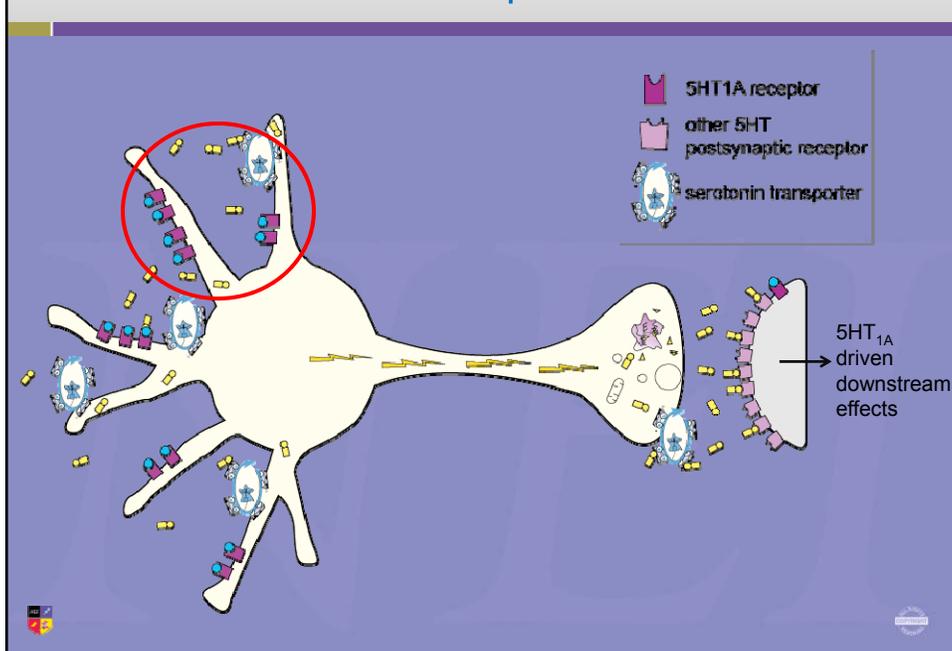


Gepirone Pharmacology

- PARTIAL agonist at *pre-synaptic* 5-HT_{1a} autoreceptors
 - Results in reduced down regulation of autoreceptors compared to SSRIs
- FULL agonist at *post-synaptic* 5-HT_{1a}
 - Results in lower 5-HT in the synapse and hence less stimulation of other 5-HT receptors and therefore lower risk of side effects compared to SSRIs and SNRIs

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Mechanism of Action of Gepirone



Gepirone has Unique Antidepressant Pharmacology

	5HT _{1A}	SRI	D ₂	Other 5HT	Other Neurotransmitter
Gepirone	✓				
Buspirone	✓		✓		
SSRIs		✓			
Vilazodone	✓	✓			
Vortioxetine	✓	✓		✓	
Lurasidone	✓		✓	✓	✓
Aripiprazole	✓		✓	✓	✓
Brexpiprazole	✓		✓	✓	✓
Quetiapine	✓		✓	✓	✓

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Gepirone Clinical Experience – Efficacy & Safety

Stephen Stahl MD, PhD

Professor of Psychiatry

University of California, San Diego

Honorary Fellow

University of Cambridge

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Summary of Individually Interpretable Trials

Study	Design	Control(s)	Endpoint	Patient #
134001	2-arm	pbo	HAMD-17	202
134002	2-arm	pbo	HAMD-17	205
134023	2-arm	pbo	HAMD-17	246
FKGBE007	2-arm	pbo	HAMD-17	238
FKGBE008	2-arm	pbo	HAMD-17	195

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Consistent Design Features of Trials

- Double-blind, placebo controlled, flexible dose, multicenter
- Moderate to severe MDD
- HAMD-17 total score ≥ 20 at screening and baseline
 - MADRS total score ≥ 30 at screening and baseline for study 134023
- Treatment duration: 8 weeks
 - 9 weeks for study 134023

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Efficacy Endpoints

- Primary
 - Mean change from baseline in total HAMD-17 at study endpoint
- Secondary endpoints
 - Change from baseline in
 - HAMD item 1 (depressed mood)
 - MADRS total score
 - CGI-S
 - Responder/Remission analyses
 - HAMD-17, HAMD-25*
 - CGI Responder
 - HAMD-17 remission

* Not examined in 134023.

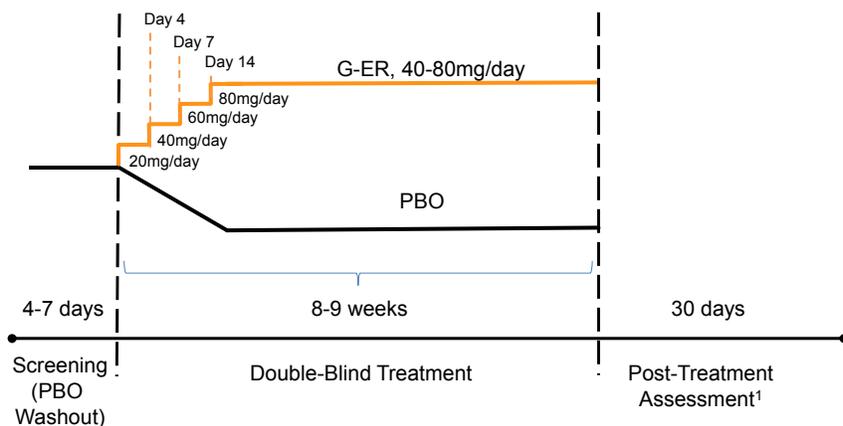
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Severity Scales Utilized

- HAMD-17: seventeen item questionnaire used to rate the severity of depression and long considered the gold standard
 - Score of 20 often a prerequisite for clinical trials
 - 2-point reduction considered clinically meaningful
 - Item 1 (mood) most important
- MADRS: ten item diagnostic questionnaire used to measure the severity of a depressive episode
 - Designed to be more sensitive to the effects of antidepressants than HAMD
 - Score of 25-30 is often a prerequisite for clinical trials
 - 2.5-point reduction is considered clinically meaningful
- CGI: seven-point scale to assess severity of a participant's current illness state (“S”) or improvement (“I”)

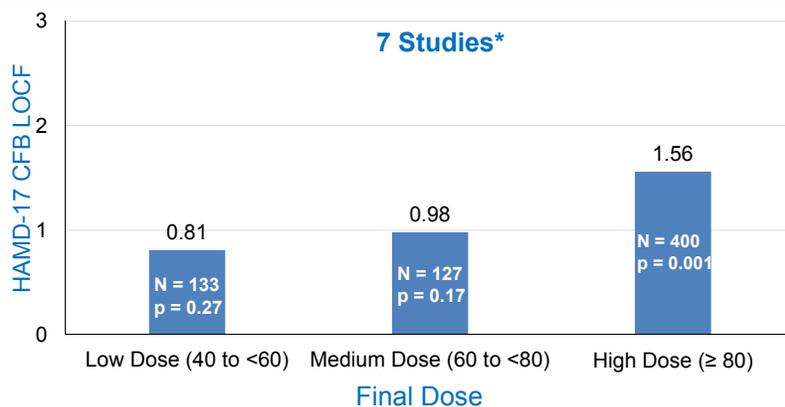
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Design of 5 Interpretable Trials



¹ Consists of AE follow-up seven days post-treatment and SAE follow-up 30 days post-treatment.

Dose Response

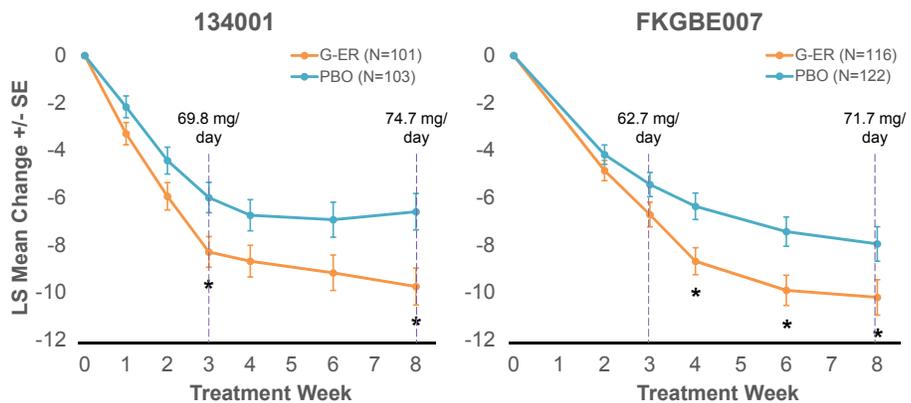


- Similar results for MADRS, HAMD14, BECH6, CGI Responders

* Five interpretable studies + 078 + 083

(Source – ISE Tables 39, 41, 42, 43)

Studies 134001 & FKGBE007: HAMD-17 (Primary Endpoint) Results



* p ≤ 0.05 vs. placebo

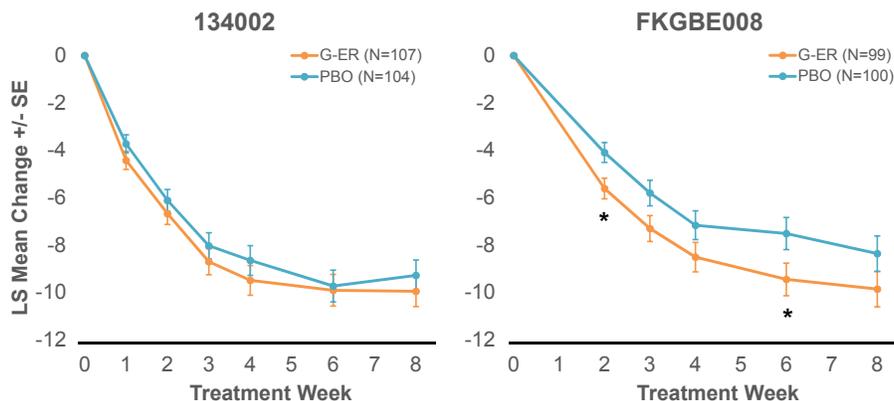
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Studies 134001 & FKGBE007: Secondary Endpoint Results

Endpoint	134001		FKGBE007	
	Mean change	p-value	Mean change	p-value
HAMD item 1	-0.39	0.005	-0.32	0.101
MADRS	-3.06	0.023	-3.78	0.008
CGI-S	-0.39	0.016	-0.38	0.015
	% subjects difference	p-value	% subjects difference	p-value
HAMD-17 responders	12.9%	0.059	16.2%	0.014
HAMD-25 responders	16.8%	0.014	18%	0.007
CGI-I responders	7.92%	0.251	13.6%	0.045
HAMD-17 remitters	13.8%	0.017	14%	0.019

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Studies 134002 & FKGBE008: HAMD-17 (Primary Endpoint) Results



* p ≤ 0.05 vs. placebo

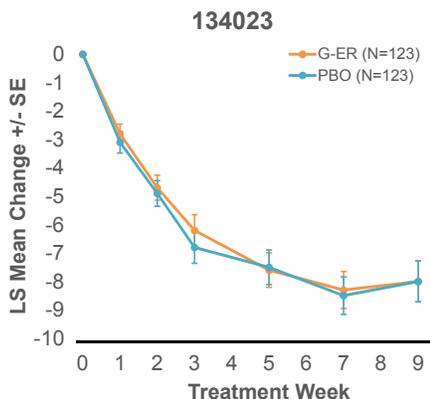
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Studies 134002 & FKGBE008: Secondary Endpoint Results

Endpoint	134002		FKGBE008	
	Mean change	p-value	Mean change	p-value
HAMD item 1	-0.18	0.036	-0.11	0.469
MADRS	-2.34	0.078	-1.86	0.208
CGI-S	-0.21	0.130	-0.19	0.275
	% subjects difference	p-value	% subjects difference	p-value
HAMD-17 responders	8.2%	0.225	6.9%	0.293
HAMD-25 responders	13.1%	0.014	14.2%	0.035
CGI-I responders	7.3%	0.297	10.1%	0.147
HAMD-17 remitters	-1.8%	0.731	7.6%	0.156

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Study 134023: HAMD-17 (Primary & Secondary Endpoint) Results



134023		
Endpoint	Mean change	p-value
HAMD item 1	0.1	0.438
MADRS	-0.8	0.572
CGI-S	0.1	0.467
%		
	subjects difference	p-value
HAMD-17 responders	-4%	0.518
HAMD-25 responders	n/a	n/a
CGI-I responders	4%	0.624
HAMD-17 remitters	-2%	0.731

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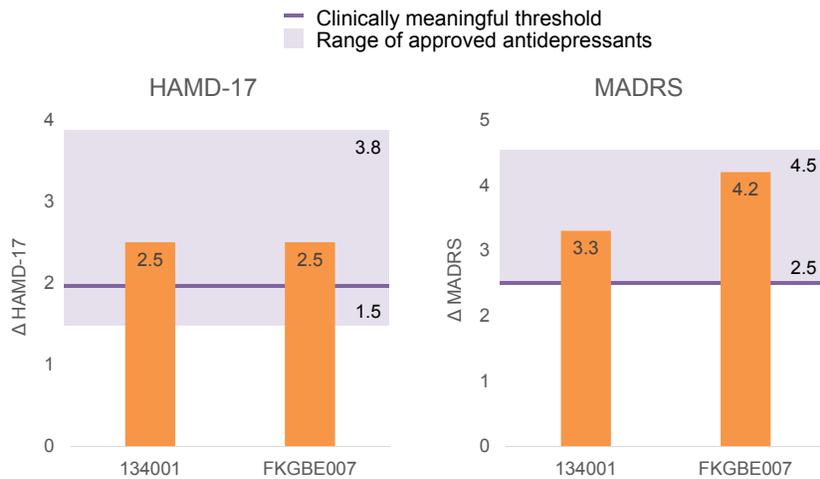
Gepirone ER Meets the Standard of Effectiveness in MDD

Trial	Primary Endpoint	Change in HAMD-17, p-value	Secondary Endpoints
134001	<i>Met primary endpoint</i>	-2.47; p=0.013	<i>Met secondary endpoints</i>
134002	Directional trend	-0.67; p=0.446	Directional trends
134023	Did not meet endpoint	0.0; p=0.947	Did not meet endpoints
FKGBE007	<i>Met primary endpoint</i>	-2.45; p=0.018	<i>Met secondary endpoints</i>
FKGBE008	Directional trend	-1.5; p=0.159	Directional trends
Meta-analysis	Favorable		Favorable

These five clinical studies are all placebo-controlled, and do not have an active comparator arm

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Effect Size of Gepirone ER vs. Approved Antidepressants



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Gepirone ER is Efficacious in MDD

- Two studies (134001 and FKGBE007) provide substantial evidence of effectiveness for gepirone ER in the treatment of MDD
 - These two studies achieved statistical significance on the primary efficacy variable, and this positive result was supported by nearly all secondary efficacy variables
 - The effect size observed with gepirone ER is clinically meaningful
- Additional supportive evidence is provided by studies 134002 and FKGBE008

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Safety of Gepirone ER

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Gepirone Safety Database

- 5868 patients are included in the safety database
 - 4976 in Phase II/III
- Safety population from 19 controlled Phase II/III ER studies includes:
 - 1,976 subjects receiving gepirone ER
 - 1,275 receiving placebo
 - 595 receiving fluoxetine
 - 276 receiving paroxetine
 - 74 receiving imipramine
- Overall, the safety profile of gepirone ER is consistent that of other antidepressants

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Gepirone ER Safety Data Set

	Gepirone N= 3117		Placebo N=2483	
	N	%	N	%
W/D Due to SAEs	77	2.5%	29	1.2%
W/D Due to AEs	509	16.3%	168	6.8%
Deaths	5	<1%	2	<1%

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Gepirone ER AEs ($\geq 5\%$)

- Dizziness
- Nausea
- Headache
- Insomnia
- Fatigue

Effects consistent with 5HT_{1A} MOA

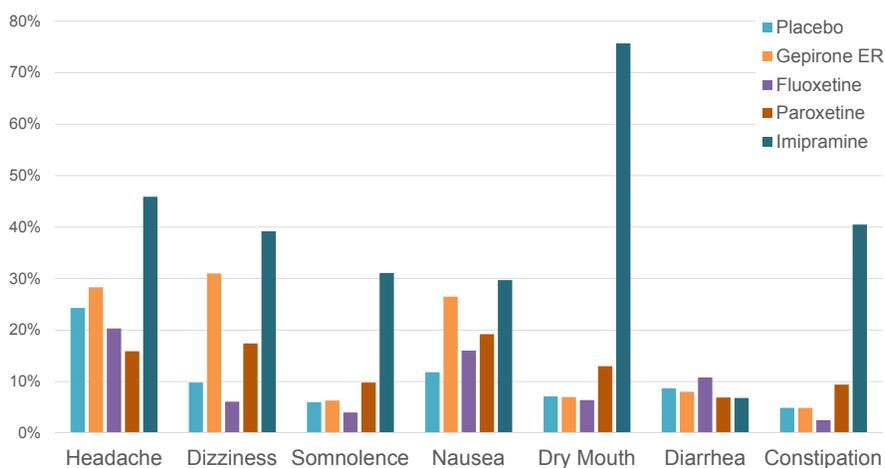
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Dizziness and Nausea

- Dizziness and nausea were typically mild to moderate with median durations of 1 and 2 days, respectively
- New dizziness and nausea events declined towards the placebo rate in the first 4-6 weeks
- Dizziness was more likely at higher doses
- Dose-response relationship was not evident for nausea
- No AEs of dizziness were coded as serious adverse events (SAEs)
 - No syncope or fainting
- 2.5% of gepirone ER patients and 0.5% of placebo patients withdrew due to dizziness

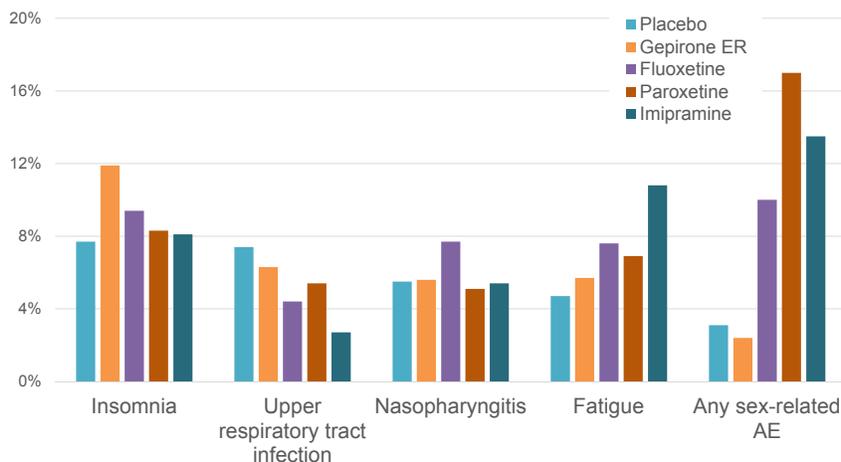
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AEs Reported by $\geq 5\%$ of Subjects in Any Treatment Group (1 of 2)



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AEs Reported by $\geq 5\%$ of Subjects in Any Treatment Group (2 of 2)



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Gepirone ER is Safe and Well-Tolerated

- Human safety data for gepirone ER is extensive
- Long-term exposure in more than 1,500 subjects has not turned up any new safety concerns
 - 692 subjects were treated for over 6 months
 - 170 subjects were treated for over 1 year
- Gepirone ER is well tolerated, with
 - Dizziness is the most common side effect,
 - typical of 5HT_{1a} agonists
- Gepirone ER has a low risk of sexual AEs and is comparable to placebo

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Overall Conclusions

- Two studies (134001 and FKGBE007) achieved statistical significance on the primary efficacy variable and nearly all secondary efficacy variables
- The effect size observed with gepirone ER is clinically relevant and comparable to other approved antidepressants
- Long-term studies exposing more than 1,500 subjects have demonstrated that gepirone ER is well tolerated

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Conclusions

Daniel Burch, MD
Vice President & Global Head,
Neuroscience
PPD

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Gepirone ER Meets Standard for Approval

- Unmet need high – new classes needed
- Safety and tolerability in keeping with general antidepressant
 - Unique AE profile of 5HT_{1a} mechanism
- Trials 001 and 007 provide substantial evidence of effectiveness
 - Met primary endpoints
 - Effect size consistent with approved antidepressants
 - Internally consistent on secondary endpoints
- Meta-analyses provide further support of efficacy
- Overall risk benefit is favorable

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TRAVIVO® [Gepirone Extended Release (ER)]

Fabre-Kramer Pharmaceuticals

Presentation to the
Psychopharmacologic Drugs Advisory Committee

December 1, 2015

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Sponsor Backup Slides

Fabre-Kramer Pharmaceuticals

Presentation to the
Psychopharmacologic Drugs Advisory Committee

December 1, 2015

Binding activity for gepirone, 3-hydroxy metabolite of gepirone, 1 PP and buspirone at alpha-adrenoreceptors

	Test Compounds											
	Gepirone			Gepirone (3-hydroxyl metabolite)			1-PP			Buspirone		
	pk ₁	n	s.e.m.	pk ₁	n	s.e.m.	pk ₁	n	s.e.m.	pk ₁	n	s.e.m.
α _{2A}	5.42	5	0.05	5.35	3	0.1	6.92	3	0.05	5.69	3	0.02
α _{2B}	4.89	5	0.07	4.69	3	0.16	6.45	3	0.03	4.90	3	0.04
α _{2C}	5.98	5	0.04	5.84	3	0.06	6.21	3	0.21	6.44	3	0.09

Adapted from Table 4, Preclinical Pharmacology of Org 33062 and its Metabolites Org 25907 and Org 33552, 2000

Gepirone and its metabolite are highly selective for 5HT_{1A} receptors

	Test Compounds			
	Gepirone	Gepirone (3-hydroxyl metabolite)	Buspirone	1-PP
	pk _i	pk _i	pk _i	pk _i
5-HT _{1A}	7.42	7.24	7.92	6.19
5-HT _{2A}	<5.20	5.70	5.62	<4.26
5-HT _{2C}	<5.03	<4.05	<5.03	<4.05
5-HT ₆	<4.30	<4.26	<4.30	<4.26
5-HT ₇	6.20	5.75	6.84	5.04

K_i affinity for gepirone, 3-hydroxy metabolite of gepirone, 1 PP and buspirone at serotonin receptors

Adapted from Table 1, Preclinical Pharmacology of Org 33062 and it's Metabolites Org 25907 and Org 33552, 2000

FDA BB Table 1 Twelve Short-Term Studies with HAMD-17 Results

Trial No.	Number of Subjects		Active Comparator, Dose range (mean dose)	Gep Doses Range (mean daily dose in mg)	Pre-Specified Primary Endpoint(s)	HAMD-17 Results ¹ (Gep.-Pbo.)		Conclusion	
	Gep.	Pbo.				LS Mean Diff ²	p-value	Division	Sponsor
FK GBE 007	116	122	None	20-80 (58.2)	HAMD-17	-2.45	0.018	Positive	
ORG 134001	101	101	None	20-80 (61.1)	HAMD-17	-2.47	0.013	Positive	
FK-GBE-008	96	99	None	20-80 (60.0)	HAMD-17	-1.38	0.20	Negative	Supportive
ORG 134002	102	103	None	20-80 (57.9)	HAMD-17	-0.71	0.42	Negative	Supportive
ORG 134023	123	123	None	20-80 (61.3)	HAMD-17	0.13	0.90	Negative	
ORG 134004	124	130	Fluoxetine 20-40 mg (34.1)	20-80 (67.1)	HAMD-25	1.04	0.18	Negative ²	Failed
ORG 134006	140	143	Paroxetine 10-40 mg (28.2)	20-80 (55.3)	HAMD-25	0.22	0.76	Negative ^{2,3}	Failed
ORG 134017	159	159	Fluoxetine 20-40 mg (25.9)	40-80 (59.7)	MADRS	0.65	0.39	Negative ²	Failed
CN105-053*	56	56	Imipramine 50-200 mg (145)	10-60 (50.4)	HAMD-17, CGI	-2.0	0.19	Negative ³	Failed
CN105-052*	35	37	Fluoxetine 20-80 mg (23.3)	20-60 (43.4)	HAMD-17, CGI	-0.69	0.74	Failed	
CN105-078*	88	47	None	10-50 (30.4) 20-100 (52.6)	HAMD-17	-1.0	0.36	Failed	
CN105-083*	73	39	None	10-50 (30.4) 20-100 (57.1)	HAMD-17	-0.49	0.75	Failed	

¹ Results were from LOCF ANCOVA including treatment and center as factors and baseline score as a covariate, with active comparator arm included in the analyses.

* Trial was terminated early.

² A lower HAMD-17 total score indicates less severe symptoms; a negative difference indicates gepirone better than placebo.

³ Active comparator beat gepirone on HAMD-17.

⁴ Active comparator beat placebo on HAMD-17.

[Source: Sample sizes were from Table 24 and Information on dose range from Table 11 and Table C4 of ISE-2007.pdf in sponsor's 2007 submission. Efficacy results are from FDA Statistical Review by Dr. Fanhui Kong]