Psychotropics in the Pipeline: Update on Emerging Trends

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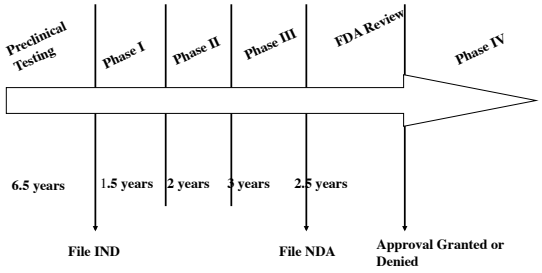
Phases of Product Development



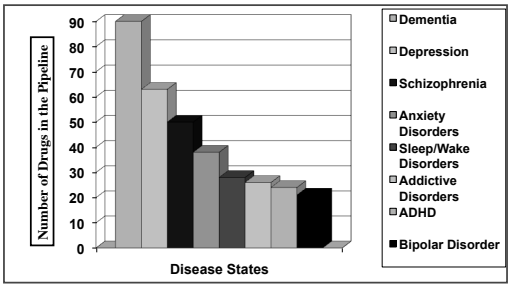
FDA Approval Process

- Pre-clinical (animal) testing
- Investigational New Drug Application (IND)
- Phase I studies (~ 20 – 80 subjects)
- Phase II studies (~ 35 – 300 subjects)
- Phase III studies (~hundreds – thousands of subjects)

FDA Approval Process (cont)

- Submission of New Drug Application (NDA)
  - FDA has 60 days to decide if it will be filed for review
- FDA evaluates safety and effectiveness
- FDA reviews information for product labeling
- FDA inspects manufacturing facility
- FDA will approve the drug or determine that it is approvable or not approvable
- Phase IV studies (after drug approved)

Psychiatric Drugs in the Pipeline



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Unmet Clinical Needs for Current Antidepressant Therapy

- Improved efficacy
- Faster onset of action
- Decreased side effect profile
  - Sexual dysfunction
  - Weight gain
  - Gastrointestinal events
- Improved medication adherence rates
- Return to normal sleep patterns
- Reduction of cognitive deficits
- Treatment of symptomatic pain accompanying depression

Drugs in the Pipeline for Depression

	Pre-Clinical	Phase I	Phase II	Phase III	NDA Filed
Antidepressant	6	13	18	4	3

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Drugs in the Pipeline for Depression

Drug Name	*Company*	*Indication*	*Phase of Development for Depression*
Desvenlafaxine (Pristiq®)	Wyeth	• MDD • GAD • Fibromyalgia • Neuropathic Pain • Vasomotor Symptoms due to Menopause	• NDA filed 12/05 • Approvable letter received 1/07
Gepirone ER	Fabre-Kramer / GSK	• MDD	• NDA filed 12/03 • Non-Approvable letter received 6/04 • Supplemental NDA filed 5/07

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Drugs in the Pipeline for Depression

Drug Name	*Company*	*Indication*	*Phase of Development for Depression*
Mifepristone (Corlux®)	Corcept Thera-peutics	• MDD with psychotic features • Dementia • Eating Disorders	• Phase III • NDA Submitted 10/06
Amibegron (SR 58611)	Sanofi-Aventis	• MDD • GAD	• Phase III • NDA Submission planned for 2008
Saredutant (SR 48968)	Sanofi-Aventis	• MDD • GAD	• Phase III • NDA Submission planned for 2008

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Drugs in the Pipeline for Depression

Drug Name	*Company*	*Indication*	*Phase of Development for Depression*
Valdoxan (agomelatine, AGO 178)	Servier / Novartis	•MDD • Anxiety •Sleep Disorders	• Phase III (US) • Refusal of Marketing Authorization (EU) 7/06 • EU Resubmission planned for 2007
Vilazodone	Clinical Data Online, Inc	• MDD	• Phase III • NDA Submission planned for 2008

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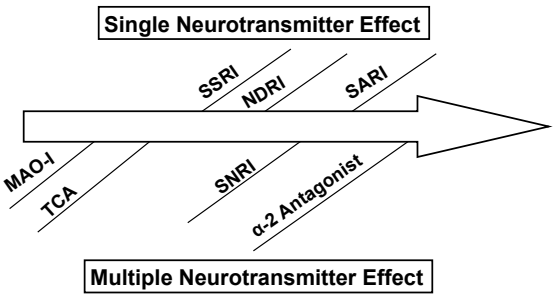
Current Antidepressant Therapy



Mechanism of Action of Investigational Antidepressants

Drug Name (Phase III)	*Pharmacology*
Desvenlafaxine (Pristiq®)	5-HT/NE Reuptake Inhibition
Gepirone ER	5-HT_{1A} Partial Agonist
Mifepristone (Corlux®)	Glucocorticoid Receptor Antagonist
Amibegron (SR 58611)	β_3 Agonist
Saredutant (SR 48968)	NK_2 Antagonist
Valdoxan (agomelatine, AGO 178)	MT_1 and MT_2 Agonist 5-HT_{2C} Antagonist
Vilazodone	5-HT Reuptake Inhibition 5-HT_{1A} Partial Agonist

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Mechanism of Action of Investigational Antidepressants

Drug Name (Phase II)	*Pharmacology*
Casopitant (GW679769)	NK_1 Antagonist
DOV 216, 303	5HT/NE/DA Reuptake Inhibitor
DOV 21,947	5HT/NE/DA Reuptake Inhibitor
Pexacerfont (BMS-562086)	CRF_1 Antagonist

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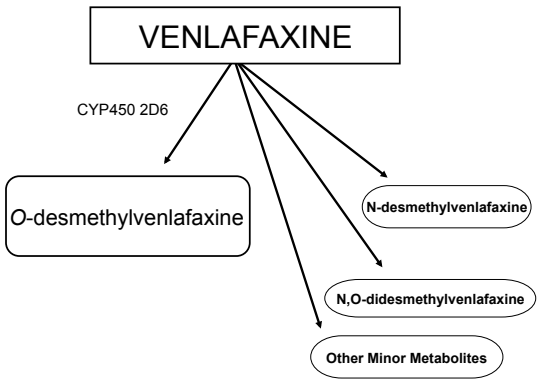
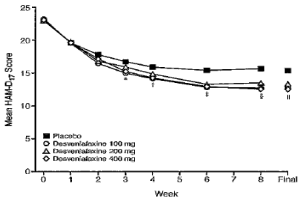


Figure 2. HAM-D_{17} Mean Scores by Week and at Final On-Therapy Evaluation

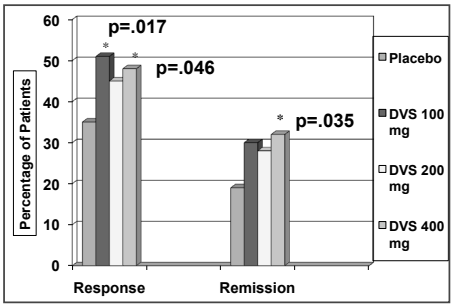


*p = .0226 desvenlafaxine 100 mg vs. placebo.
†p = .0497 desvenlafaxine 100 mg vs. placebo.
‡p = .0028 desvenlafaxine 100 mg vs. placebo, p = .0500 desvenlafaxine 200 mg vs. placebo, p = .0060 desvenlafaxine 400 mg vs. placebo.
§p = .0016 desvenlafaxine 100 mg vs. placebo, p = .0008 desvenlafaxine 400 mg vs. placebo.
‖p = .0038 desvenlafaxine 100 mg vs. placebo, p = .0023 desvenlafaxine 400 mg vs. placebo.
Abbreviation: HAM-D_{17} = 17-item Hamilton Rating Scale for Depression.

DVS (Pristiq®) - Efficacy Acute Treatment

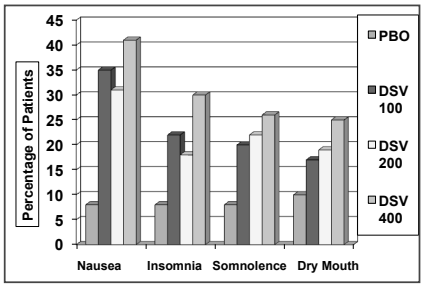
J Clin Psychiatry 2007;68:677-688.

Desvenlafaxine (Pristiq®) – Efficacy Acute Treatment



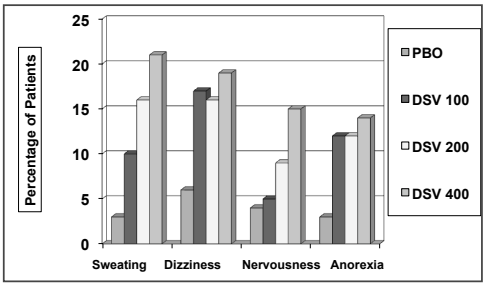
J Clin Psychiatry 2007;68:677-688.

Desvenlafaxine (Pristiq®) – Tolerability Acute Treatment



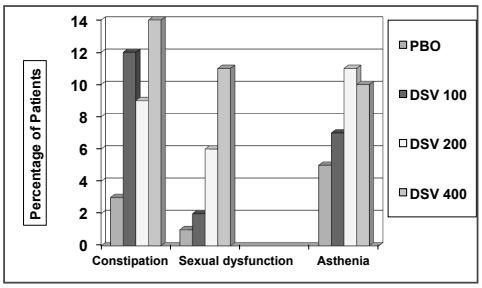
J Clin Psychiatry 2007;68:677-688.

Desvenlafaxine (Pristiq®) – Tolerability Acute Treatment



J Clin Psychiatry 2007;68:677-688.

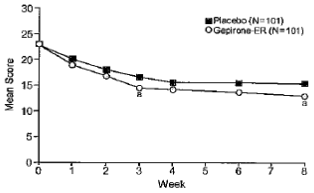
Desvenlafaxine (Pristiq®) – Tolerability Acute Treatment



J Clin Psychiatry 2007;68:677-688.

Gepirone ER – Efficacy Acute Treatment

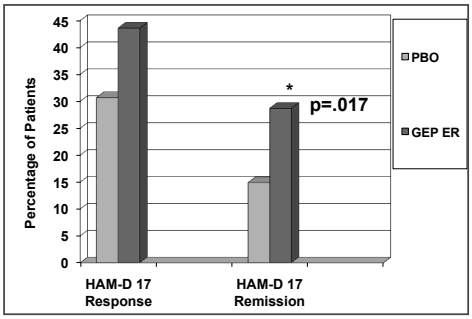
Figure 1. HAM-D-17 Scores From Baseline to Endpoint (LOCF)



[a]Significant at $p \leq .05$ by least-squares means analysis of variance.
Abbreviations: ER = extended release, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, LOCF = last observation carried forward.

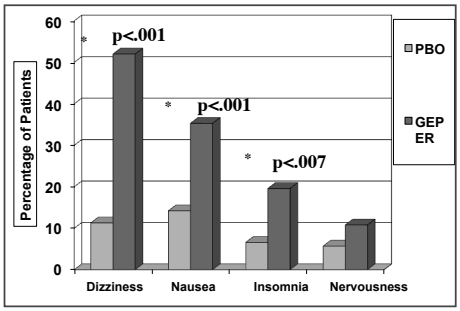
J Clin Psychiatry 2003;64:243-249.

Gepirone ER – Efficacy Acute Treatment



J Clin Psychiatry 2003;64:243-249.

Gepirone ER – Tolerability Acute Treatment



J Clin Psychiatry 2003;64:243-249.

Gepirone ER – Relapse Prevention

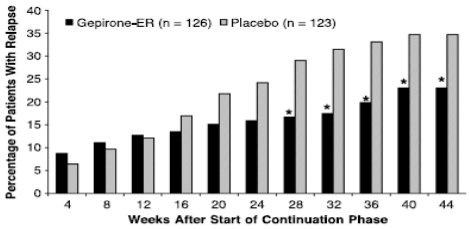


FIGURE 1. Percentage of patients with relapse of depression during the continuation phase based on the intent-to-treat, last-observation-carried-forward population. *$P \leq 0.05$.

J Clin Psychopharmacol 2005;25:79-84.

Mifepristone (Corlux®) – Mechanism of Action

- **Differences between Psychotic Major Depression (PMD) and MDD**
  - **Neuropsychological testing**
  - **Response to treatment**
  - **Morbidity and mortality**
  - **↑ HPA Axis activity**
    - ➢ **↑ urinary free cortisol levels**
    - ➢ **↑ evening and night time cortisol levels**
    - ➢ **high rates of dexamethasone nonsuppression**
- **Hypothesis → Psychotic features associated with PMD due to ↑ glucocorticoid activity**

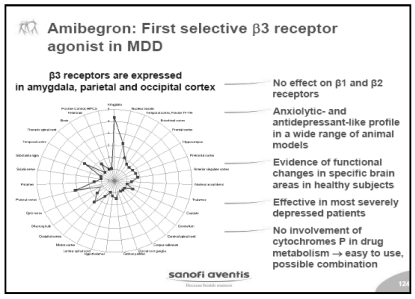
Neuropsychopharmacology 2006;31:628-636.

Mifepristone (Corlux®) – Efficacy

- **Published literature**
  - **1 Case Series 2001 (N=5)**
    - ➢ **(+) benefit based on HAM-D and BPRS**
  - **2 Open Label Studies 2002 (N=30) and 2005 (N=20)**
    - ➢ **2002 → BPRS:**
      - **13/19 demonstrated ≥ 30% reduction**
      - **12/19 demonstrated ≥ 50% reduction on positive symptom subscale**
    - ➢ **2002 → HAM-D 21**
      - **8/19 demonstrated ≥ 50% reduction**
    - ➢ **2005 → HAM-D 21, BPRS and CGI**
      - **significant improvement seen on all measures**

J Clin Psychopharmacol 2001;21:516-521.,
Biol Psychiatry 2002;52:386-392., J Clin Psychiatry 2005;66:598-602.

Amibegron – Mechanism of Action



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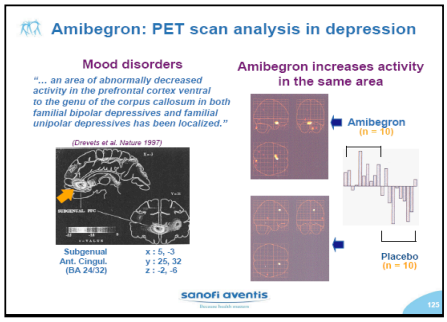
Amibegron – Mechanism of Action



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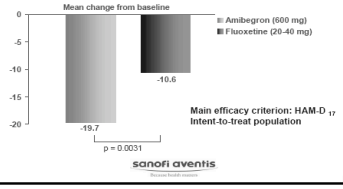
Amibegron – Efficacy Acute Treatment

In one phase II study, amibegron was more effective than fluoxetine in patients with depression associated with melancholic features

Completed trial in MDD: Key efficacy results

- Patients with recurrent major depression and melancholia; n=32; 6 weeks duration



Main efficacy criterion: HAM-D 17
Intent-to-treat population

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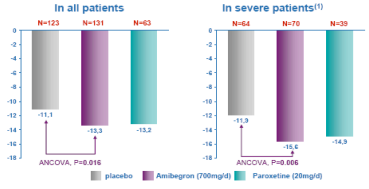
Amibegron – Efficacy Acute Treatment

Amibegron in MDD:
Key findings from completed phase III trial

EFC5374: In- and out-patients with recurrent major depression

HAM-D 17: *Change from baseline to Day 42 (LOCF)*



(1) HAM-D>25 at baseline
HAM-D 17 = Hamilton rating scale for depression
LOCF=Last observation carried forward

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Amibegron – Tolerability Acute Treatment

Amibegron displays a good safety profile

EFC5374 and EFC5379: Incidence of patients (%) with common emergent AEs (≥ 5% in both studies)

Percentage	Placebo N=244	Amibegron 700 mg/day N=255	Paroxetine 20 mg/d N=124
Any event	47.1	47.5	55.6
Nausea	4.5	9.4	10.5
Dry mouth	4.9	3.5	8.1
Headache	9.8	11.0	8.1
Dizziness	2.0	3.1	6.5

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Amibegron

Amibegron: On-going phase III program

MDD and GAD in parallel

Indication	Purpose	Study Number	Study name	No. of patients	Status / Results
MDD	Acute efficacy	EFC5041	Orion	458	2Q2007
MDD	Acute efficacy	EFC5116	Phoenix	476	2Q2007
MDD	Long term safety	LTS4848	Rubicon	527	2Q2007
MDD	Acute efficacy, elderly	EFC4846	Zephir	280	3Q2007
MDD	Acute efficacy, dose ranging	EFC6607	Sirius	660	1-2Q08
MDD	Maintenance efficacy	LTE5376	Calypso	400	3Q2008
GAD	Acute efficacy	EFC5892	Libra	360	2Q2007
GAD	Acute efficacy	EFC5893	Aquarius	366	2Q2007
GAD	Acute efficacy, dose ranging	EFC5891	Electra	480	3Q2007
GAD	Maintenance efficacy	LTE5894	Vega	340	1Q2009
GAD	Acute efficacy, elderly	EFC5895	Gemini	270	Start planned 1Q07

MDD – Major Depressive Disorder
GAD – Generalized Anxiety Disorder

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Tachykinins

- **Family of neuropeptides**
  - **In humans referred to as neurokinins**
    - **Substance P**
    - **Neurokinin A**
    - **Neurokinin B**
- **Three categories of neurokinin receptors**
  - **NK_1 Greatest affinity for Substance P**
  - **NK_2 Greatest affinity for Neurokinin A**
  - **NK_3 Greatest affinity for Neurokinin B**

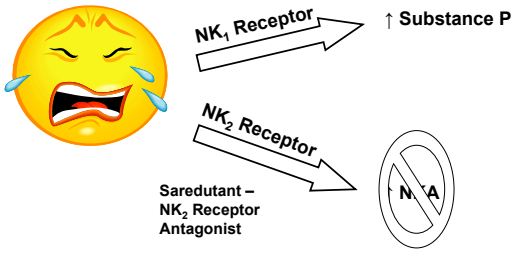
Devane CL. Pharmacotherapy 2001(9):1061-1069
Current Pharmaceutical Design 2005;11:1529-1547.

Role of Tachykinins in Depression and Anxiety

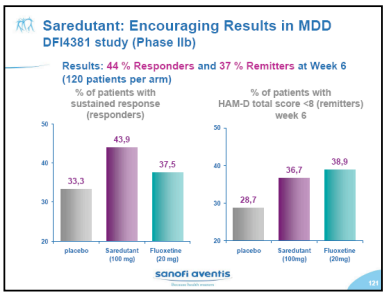
NK_1 Receptor → ↑ Substance P

NK_2 Receptor → ↑ NKA

Saredutant – Mechanism of Action



Saredutant – Efficacy Acute Treatment



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Saredutant – Tolerability Acute Treatment

Saredutant in MDD
Safety in Phase III completed studies

A significant benefit versus paroxetine

Incidence of patients (%) with common emergent AEs (≥5% in all studies)

	Placebo (N=607)	Saredutant (N=623)	Paroxetine (N=607)
Any event	61.6%	61.5%	72.2%
Nausea	6.8%	6.1%	14.8%
Dry mouth	5.6%	7.2%	9.9%
Diarrhoea	4.3%	3.7%	8.2%
Headache	15.5%	14.6%	15.7%
Somnolence	2.6%	2.4%	9.9%
Dizziness	4.8%	5.6%	6.9%

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Saredutant

Saredutant: On-going phase III studies

First in MDD, then in GAD

Indication	Purpose	Study number	No. of patients	Status/Results
MDD	Long term safety	LTS5577	360	2Q2007
MDD	Abrupt withdrawal	SFY6577	88	4Q2007
MDD	Long term efficacy	EFC5576	400	On-going (data 2008)
MDD	Acute efficacy, elderly	EFC5574	375	On-going (data 2008)
GAD	Acute efficacy	EFC5581	360	started in 4Q2006
GAD	Acute efficacy	EFC5582	405	started in 4Q2006
GAD	Acute efficacy	EFC5583	360	started in 4Q2006
GAD	Acute efficacy, elderly	EFC6757	300	To be started in 2007
GAD	Long term efficacy	EFC5586	340	To be started in 2007

MDD - Major Depressive Disorder
GAD – Generalized Anxiety Disorder

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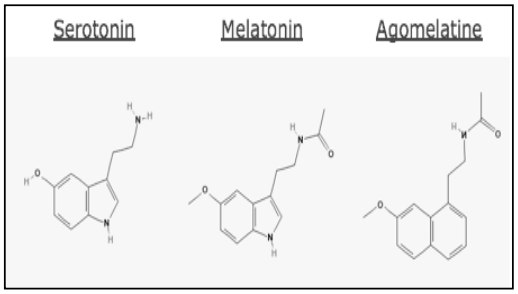
Valdoxan (Agomelatine) – Mechanism of Action



Valdoxan (Agomelatine) – Efficacy Acute Treatment

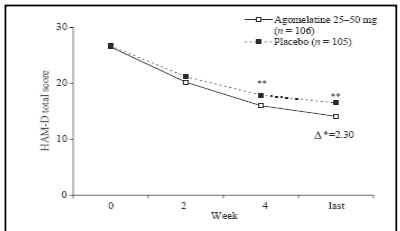
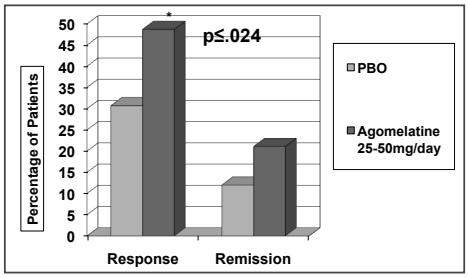


Figure 2 HAM-D total scores over time in full ITT population. *Adjusted on centre and baseline, last observation carried forward. **$p < 0.05$.

Eur Neuropsychopharmacol 2006;16:93-100.

Valdoxan (Agomelatine) – Efficacy Acute Treatment



Eur Neuropsychopharmacol 2006;16:93-100.

Valdoxan (Agomelatine) – Effect on Sleep

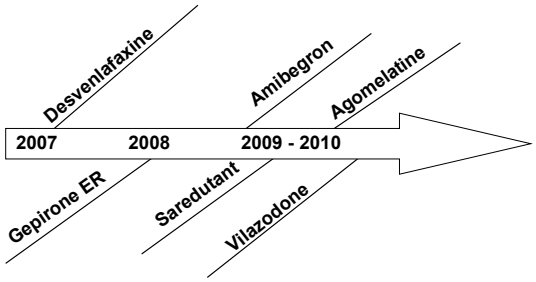
- Agomelatine 25-50mg/day vs. Venlafaxine 75-150mg/day
  - HAM-D scores at 6 weeks
    - 9.9 ± 6.6 agomelatine vs. 11.0 ± 7.4 venlafaxine
  - LEEDS Sleep Evaluation Questionnaire (LSEQ)
    - LSEQ "getting to sleep" (GTS) at W1 and W6: agomelatine > venlafaxine (p=.007;p=.001)
    - LSEQ "quality of sleep" (QOS) at W1 and W6: agomelatine > venlafaxine (p=.015;p=.021)
  - Visual Analogue Scale
    - "daytime sleepiness" and "feeling good" at W1: agomelatine > venlafaxine (p≤.001)

Eur Neuropsychopharmacol 2006;16:93-100.

Vilazodone

- MOA → SSRI + 5-HT_{1A} partial agonist
- "Targeted Antidepressant"
- Genetic biomarkers developed in parallel with drug development
- PGxPredict Test (pharmacogenetic test) will be co-marketed with drug

Antidepressant Timeline



Unmet Clinical Needs for Current Antipsychotic Therapy

- Improved overall efficacy
- Improved efficacy for negative symptoms
- Improved efficacy for cognitive symptoms
- Decreased side effect profile
  - metabolic side effects (weight gain, diabetes, hyperlipidemia)
  - EPS
  - TD
  - hyperprolactinemia
  - sexual dysfunction
  - sedation
- Improved medication adherence rates

Drugs in the Pipeline for Psychosis/Schizophrenia

	Pre-Clinical	Phase I	Phase II	Phase III	NDA Filed
Antipsychotic	4	12	15	2	2

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Drugs in the Pipeline for Psychosis/ Schizophrenia

Drug Name	*Company*	*Indication*	*Phase of Development for Psychosis/ Schizophrenia*
Bifeprunox (DU-127090)	Solvay, Wyeth	• Schizophrenia	• Non-approvable letter received 8/07
Zomaril (Iloperidone)	Vanda Pharmaceuticals	• Schizophrenia • Bipolar Disorder	• NDA filed 9/07
Asenapine (ORG5222)	Organon	• Schizophrenia • Bipolar Disorder	• Phase III • NDA submission planned for 2008
Ocaperidone	Evotec	• Schizophrenia	• Phase III

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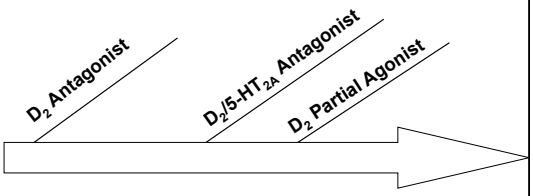
Current Antipsychotic Therapy



Mechanism of Action of Investigational Antipsychotics

Drug Name (Phase III)	*Pharmacology*
Bifeprunox (DU-127090)	D_2 Partial Agonist 5-HT_{1A} Partial Agonist
Zomaril (Iloperidone)	D_2 Antagonist 5-HT_{2A} Antagonist
Asenapine (ORG5222)	D_2 Antagonist 5-HT_{2A} Antagonist
Ocaperidone	D_2 Antagonist 5-HT_{2A} Antagonist

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Mechanism of Action of Investigational Antipsychotics

Drug Name (PHASE II)	*Pharmacology*
ORG 34517/34850	Glucocorticoid receptor type II (GRII) antagonist
ORG 24448	AMPA modulator
Lu-35-138	D_4 Antagonists 5-HT_{2A} Antagonist
ACP-104	Metabolite of clozapine
Talnetant (SB-223412)	NK-3 Antagonist
P-101	Alpha-2-adrenoceptor antagonist
ORG 25935	GLYT1 (glycine transporter) inhibitor
AVE 1625	CB1 Antagonist

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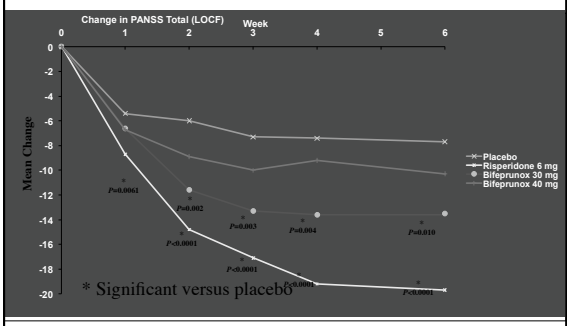
Bifeprunox

- D_2 Partial Agonist / 5-HT_{1A} Partial Agonist
- No affinity for 5-HT_{2A}, 5-HT_{2C}, M_1, H_1, α_1 receptors
- FDA Non-Approvable letter content:
  - acknowledged (+) effectiveness in one maintenance study
  - 2nd positive maintenance study needed to support maintenance claim
  - bifeprunox separated from placebo in 2 acute, short-term studies
  - efficacy data in 2 acute, short-term studies when compared to reference drugs were not sufficient for approval
  - further data needed regarding metabolism of bifeprunox
  - further information needed regarding 1 death in clinical trials

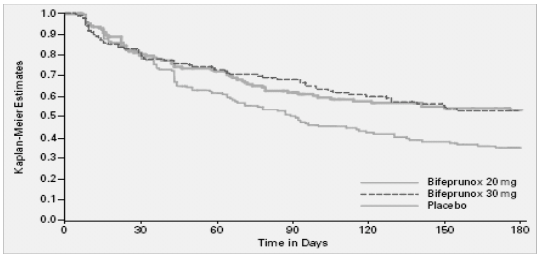
Bifeprunox – Efficacy - Acute Treatment



Pairwise comparisons between risperidone and placebo were based on a model including all treatment groups, but using only the contrast for risperidone versus placebo

Meltzer et al. 2007.

Bifeprunox - Time From Randomization to Deterioration

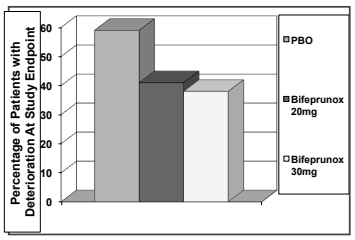


	PBO		BX 20 mg		BX 30 mg	
Number of Patients	166		159		172	
Number of Relapses	98	(59.0%)	64	(40.3%)	66	(38.4%)

Bourin , et al. 2007.

Bifeprunox – Efficacy Maintenance Treatment

- **Time to deterioration – significantly longer with bifeprunox 20mg (p=.008) and 30mg (p=.006) vs. placebo**
- **Risk of deterioration - 1.5x higher with placebo vs. bifeprunox 20mg and 30mg**



Poster – 2007 International Congress on Schizophrenia Research.

Bifeprunox – Tolerability

	HPDL	CLOZ	RISP	OLZ	QTP	ZIP	ARIP	PALI	BIFEP
EPS*	+++	0	+	0/+	0	0/+	0/+	+	0
Weight gain/ Endocrine	+	+++	++	+++	++	0/+	0/+	++	0
Anticholinergic	0	+++	0/+	+/++	0/+	0/+	0	0/+	0
Hematological	0	+++	0	0	0	0	0	0	0
Cardiovascular	+	0/+	+	+	+	++	0	+	0/+
Prolactin	++	0/+	+++	0/+	0/+	0/+	0	+++	0
Sedation	+	+++	+	+/++	++	++	+	+	+

*At appropriate doses; 0 = none; + = mild; ++ = moderate; +++ = substantial

Adapted from Masand PS et al. 1998.

Zomaril (Iloperidone) – Phase III Clinical Trials

Trial Number	N	Doses*	PANSS Improvement	Outcome (Significance vs. PBO)
LILP 3000	621	PBO ILO 4mg/day ***ILO 8mg/day*** ***ILO 12mg/day***	-4.6 -9.0 ***-7.8*** ***-9.9***	N/A NS ***NS*** ***P<.05***
LILP 3004	616	PBO 4-8mg/day ***10-16mg/day***	-3.5 -9.4 ***-11.1***	N/A p<.02 ***p<.001***
LILP 3005	710	PBO ***12-16mg/day*** 20-24mg/day	-7.6 ***-11.0*** -14.0	N/A ***NS*** p<.01

*** Declared dose (dose for which the drug must show statistically significant improvement vs. PBO)**

www.vandapharma.com

Zomaril (Iloperidone) – Additional Clinical Issues

- **QT_C prolongation**
- **Long-term studies**
  - **Three 52-week studies completed**
  - **Iloperidone doses 4-16mg/day**
  - **Time to discontinuation similar to haloperidol**
- **Long-Acting Injectable Formulation**
  - **completed Phase I/IIa safety trial**
  - **dosing every 4 weeks**
- **Genetic Testing**
  - **efficacy**
  - **QT_C prolongation**

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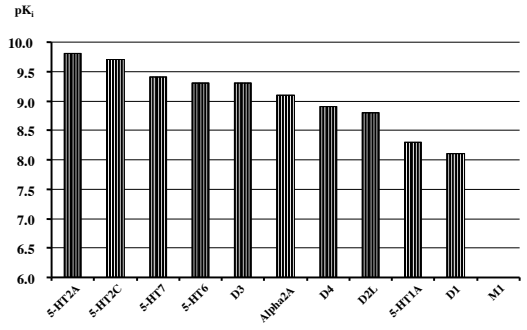
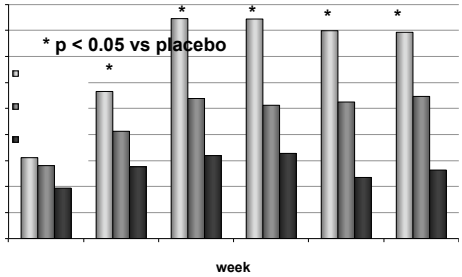
Asenapine – Receptor Binding Profile



Data on File: Organon

Asenapine - PANSS Total

Absolute Change from Baseline (ITT, LOCF)



(Baseline Total PANSS: asenapine = 96.5, risperidone = 92.2, placebo = 92.4)

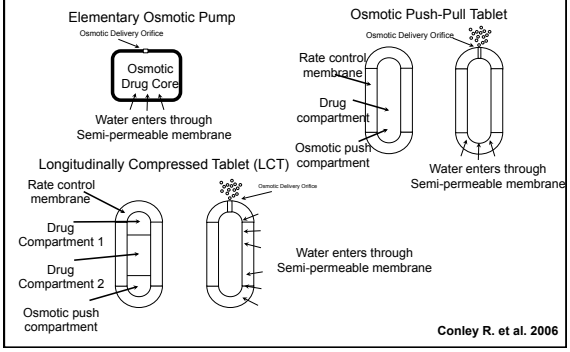
Data on File: Organon

Antipsychotic Agents and Formulations

Drug	IR Tabs/ Caps	IM	Depot IM	Solution	Quick Dissolve	SR
Clozapine	Yes	No	No	No	Yes	No
Olanzapine	Yes	Yes	Yes**	No	Yes	No
Quetiapine	Yes	No	No	No	No	Yes
Risperidone	Yes	No	Yes	Yes	Yes	No
Ziprasidone	Yes	Yes	Yes**	No	No	No
Aripiprazole	Yes	Yes	Yes**	Yes	Yes	No
Paliperidone	No	No	Yes**	No	No	Yes

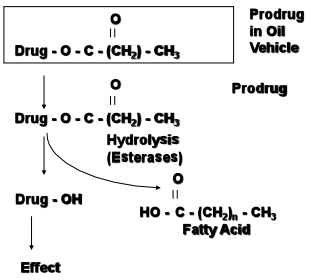
**** In development – not FDA-approved**

OROS Technology - Invega

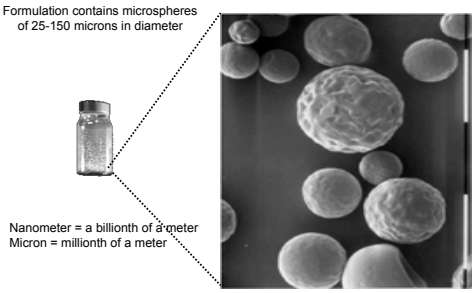


Conley R. et al. 2006

Depot Formulations of Conventional Antipsychotics



Risperidone Microspheres



Antipsychotic Long-Acting Injectables (LAI) in the Pipeline

- Olanzapine Pamoate
  - Phase III
  - Dosing Interval → 2 and 4 weeks
  - NDA Submission planned for 2007/2008
- Paliperidone Palmitate
  - Phase III
  - Dosing Interval → 4 weeks
  - NDA Submission planned for 2007/2008
- Aripiprazole Pamoate
  - Phase II
  - Dosing Interval → Unknown
- Iloperidone
  - Phase II
  - Dosing Interval → 4 weeks

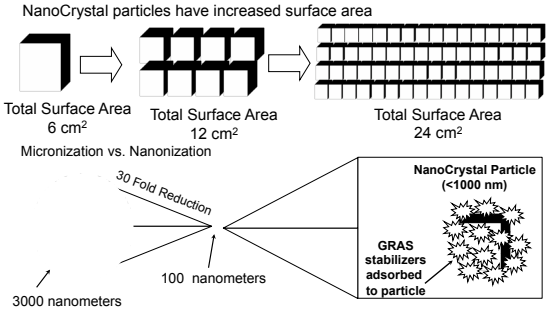
Nanotechnology

- Dispersion of small particles (< 1000 nm)
- Allows delivery of relatively insoluble drugs
- Parenterally - lower volumes, longer delivery rates
- Liposomes
- Targeted drug delivery

Kabanov AV, et al. 2004; Lockman PR, et al. 2002; Sahoo SK, et al. 2003

NanoCrystal Technology

NanoCrystal particles have increased surface area



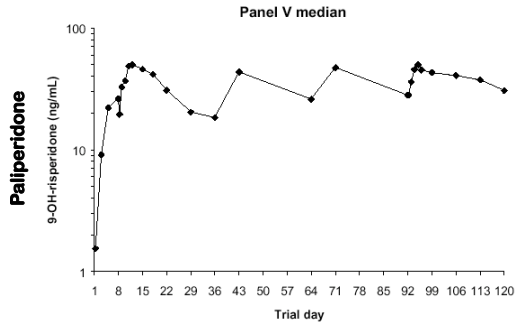
www.elan.com

9-OH Risperidone Palmitate (R092670)

- 9-hydroxy-risperidone palmitate depot formulation is an aqueous suspension - of crystals with specific surface areas
- NDA to be filed
  - First study in USA, Phase IIa- scheduled at Univ of Texas
  - Objectives:
    - Evaluate route of injection - deltoid v. gluteus
    - Demonstrate sustained and stable levels of 9-hydroxy-risperidone during each treatment cycle
- Formulation to be administered Qmonth
- Loading dose first month to be used
  - 2x maintenance
    - Evaluated as 2x single injection or
    - 2 injections 1 week apart

Ereshefsky L 2002, Ereshefsky L 2006

First injection of 150 mg, 1 week later repeat 150 mg later, then 150 mg @ monthly injections



Ereshefsky L 2002, Ereshefsky L 2006

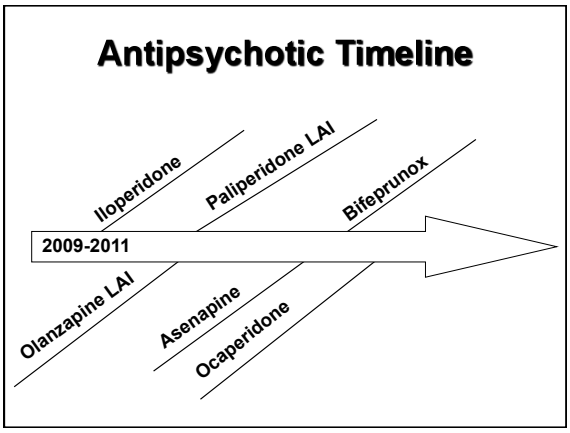
Preliminary Data: 9-OH Risperidone

- Mean Cmax were reached after approximately 10 to 13 days for the different doses
  - At 4 weeks post-injection the peak to trough fluctuation at steady-state was on average 1.6
- Steady-state is reached after the 4th injection
  - ➢ Peak plasma levels at steady-state were about 1.5 times higher than those after a single dose
  - Mean plasma levels fell to within the range usually seen on an oral dose of 2 mg risperidone
- Dosing: 1-6 mg 'equivalent' to 25, 50, 100, 150 mg IM (volumes of 0.25, 0.5, 1 or 1.5 ml)

Ereshefsky L 2002, Ereshefsky L 2006

Issues That Need Further Exploration with New Dosage Forms

- How does dosage form change pharmacodynamics?
  - Cp max
  - Cp min
  - Ratio of active metabolites - interconversion of isomers
  - Brain transport of drug
- How does this impact clinical decisions?
  - Patient selection
  - Tolerability
  - Dosage conversion
  - Long-term side effects
  - Pharmacoeconomic benefit
  - Progression of illness
  - Other potential uses of agents


Antipsychotic Timeline
Iloperidone
Paliperidone LAI
Bifeprunox
2009-2011
Olanzapine LAI
Asenapine
Ocaperidone