UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d) of
the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): May 18, 2009

VANDA PHARMACEUTICALS INC.

(Exact name of Registrant as specified in its charter)

Delaware
(State or other jurisdiction of incorporation)

000-51863	**03-0491827**
(Commission File No.)	(IRS Employer Identification No.)

9605 Medical Center Drive
Suite 300
Rockville, Maryland 20850
(Address of principal executive offices and zip code)

Registrant's telephone number, including area code: (**240) 599-4500**

Not Applicable
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

o Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

o Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

o Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

o Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Item 8.01. Other Events

Vanda Pharmaceuticals Inc. (the "Company" or "Vanda") will make presentations regarding the Company's product, Fanapt™ (iloperidone), to medical professionals, analysts, investors and others at the Annual Meeting of the American Psychiatric Association (the "APA Meeting") on May 18, 2009 and May 20, 2009. The posters that will be used for the May 18, 2009 presentations are furnished as Exhibit 99.1 to this Form 8-K. In addition, the posters will be posted on the Company's Web site http://www.vandapharma.com.

On May 14, 2009, the Company issued a press release regarding its participation at the APA Meeting and disclosing certain of the data to be presented by the Company at the APA Meeting. The full text of this press release is furnished as Exhibit 99.2 to this Form 8-K.

Various statements to be made in the presentations, including statements in the posters furnished as Exhibit 99.1 to this Form 8-K, and statements made in the press release furnished as Exhibit 99.2 to this Form 8-K, are "forward-looking statements" under the securities laws. Words such as, but not limited to, "believe," "expect," "anticipate," "estimate," "intend," "plan," "targets," "likely," "will," "would," and "could," and similar expressions or words, identify forward-looking statements. Forward-looking statements are based upon current expectations that involve risks, changes in circumstances, assumptions and uncertainties. Vanda is at an early stage of development and may not ever have any products that generate significant revenue. Important factors that could cause actual results to differ materially from those reflected in the Company's forward-looking statements include, among others: delays in the completion of Vanda's clinical trials; a failure of Vanda's products to be demonstrably safe and effective; Vanda's failure to obtain regulatory approval for its products or to comply with ongoing regulatory requirements for its products; a lack of acceptance of Vanda's products in the marketplace, or a failure to become or remain profitable; Vanda's expectations regarding trends with respect to its costs and expenses; Vanda's inability to obtain the capital necessary to fund its commercial and research and development activities; Vanda's failure to identify or obtain rights to new products; Vanda's failure to develop or obtain sales, marketing and distribution resources and expertise or to otherwise manage its growth; a loss of any of Vanda's key scientists or management personnel; losses incurred from product liability claims made against Vanda; a loss of rights to develop and commercialize Vanda's products under its license and sublicense agreements and other factors that are described in the "Risk Factors" section (Part II, Item 1A) of Vanda's quarterly report on Form 10-Q for the fiscal quarter ended March 31, 2009 (File No. 001-34186). In addition to the risks described above and in Part II, Item 1A of Vanda's quarterly report on Form 10-Q, other unknown or unpredictable factors also could affect Vanda's results. There can be no assurance that the actual results or developments anticipated by Vanda will be realized or, even if substantially realized, that they will have the expected consequences to, or effects on, Vanda. Therefore, no assurance can be given that the outcomes stated in such forward-looking statements and estimates will be achieved.

All written and verbal forward-looking statements attributable to Vanda or any person acting on its behalf are expressly qualified in their entirety by the cautionary statements contained or referred to herein. Vanda cautions investors not to rely too heavily on the forward-looking statements Vanda makes or that are made on its behalf. The information in this release is provided only as of the date of this release, and Vanda undertakes no obligation, and specifically declines any obligation, to update or revise publicly any forward-looking statements, whether as a result of new information, future events or otherwise.

The information in the posters attached as Exhibit 99.1 to this Form 8-K and the information in the press release attached as Exhibit 99.2 to this Form 8-K will be provided only as of the applicable dates on which such posters are presented and such press release is issued, and the Company undertakes no obligation to update any forward-looking statements contained in such posters or press release from and after the dates of such presentations or issuance whether as a result of new information, future events or otherwise.

The information in Item 8.01 of this Form 8-K, the posters attached as Exhibit 99.1 to this Form 8-K and the press release attached as Exhibit 99.2 to this Form 8-K shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Presentation posters.
99.2	Press Release of Vanda Pharmaceuticals Inc. dated May 14, 2009.

NR1-092

Selective Estrogen Receptor Modulators Share the Antipsychotic Gene Expression Profile, Suggesting Their Potential in the Treatment of Schizophrenia

Andrew Thompson, BS; Christian Lavedan, PhD; Simona Volpi, PhD; Louis Licamele, MS; Shruti Mitkus, PhD; Kendra Mack, MS; Mihael H. Polymeropoulos, MD.

Vanda Pharmaceuticals Inc., Rockville, MD

Abstract

Objective: A possible protective effect of estrogen has been proposed for schizophrenia based on the observation that, relative to men, women show a delay in disease onset age with a second onset peak after age 44 years. Recently, DNA variants which may contribute to the risk of developing schizophrenia have been identified in the estrogen receptor alpha gene. Several clinical studies have shown that the selective estrogen receptor modulator (SERM) tamoxifen can reduce mania symptoms in patients with bipolar disorder. Symptoms of psychosis and cognitive functioning were also shown to improve in women affected with schizophrenia who were treated with oestradiol or raloxifene. To better understand the effect of SERMs at the molecular level, their impact on the expression of the human genome was evaluated.

Methods: The gene expression group profile of tamoxifen, raloxifen and clomiphene was determined in a cell line by analyzing the up- and down-regulation of 12,490 genes. Truncated Kolmogorov-Smirnov (KS) statistics were used to compare the SERM gene signature with that of a library of 463 drugs used to treat a variety of disorders.

Results: It was discovered that the gene expression signature of the SERMs was the most similar to that of the antipsychotics, as compared to all other drug group profiles. SERMs affect lipid homeostasis in a manner similar to antipsychotics (KS scores of 0.997 and 0.806 for the top 20 and 100 probe sets, respectively). A number of genes up-regulated by both SERMs and antipsychotics were Sterol Regulatory Element Binding Proteins (SREBP) responsive genes in the cholesterol biosynthetic pathway, which have been shown to be activated by the modulation of the estrogen receptor.

Conclusions: These results support an antipsychotic therapeutic effect of SERMs, possibly through the alteration of lipid homeostasis. Vanda Pharmaceuticals sponsored this study.

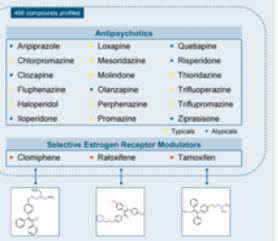
Introduction

- It has been suggested that estrogen levels play a role in the etiology and/or the severity of schizophrenia symptoms
- A possible protective effect of estrogen has been proposed based on the observation that, relative to men, women show a delay in onset age of schizophrenia, with a second onset peak after age 44 years[1]
- Symptoms in women affected with schizophrenia have been shown to frequently vary with the menstrual cycle, and to worsen during phases of low estrogen[1]
- It has been reported that dopamine can activate estrogen receptors[2]
- DNA variants which may contribute to the risk for schizophrenia have recently been identified in the estrogen receptor alpha gene (*ESR1*)[3]
- Several clinical studies have shown that tamoxifen can reduce mania symptoms in patients with bipolar disorder[4,5]
- Symptoms of psychosis and cognitive functioning were also shown to improve in women affected with schizophrenia who were treated with oestradiol or raloxifene[6]
- To gain insights into the mechanism of action of drugs, we studied the expression profile of 12,490 human genes in a cell line treated with a library of 466 compounds used in a variety of disorders, including 18 antipsychotics and 3 selective estrogen receptor modulators (SERMs) (Figure 1)

Supported by funding from Vanda Pharmaceuticals Inc.

- We have discovered a common effect of antipsychotics on the biosynthesis and regulation of fatty acids and cholesterol that is shared by the group of SERMs, which included tamoxifen, raloxifene, and clomiphene
- These results support an antipsychotic therapeutic effect of SERMs, possibly through the alteration of lipid homeostasis

Figure 1. Profiled Antipsychotics and Selective Estrogen Receptor Modulators



Methods

Cell Culture and Drug Treatment

- Retinal pigment epithelia cell line, ARPE-19/HPV-16
  - human origin
  - normal karyotype
  - easily grown as monolayer in 96-well plates (~2x10e5 cells/well)
  - expresses the dopamine receptor D2, the serotonin receptors 1A, 2A, and 2C, the muscarinic receptor M3, and the histamine receptor H1
- Cell line from glioblastoma origin (H4) used only for independent replication
- 24 hrs incubation before treatment with 10μM drug or vehicle

Gene Expression Profiles

- RNA extracted after 24 hrs treatment
- 708 U133A2.0 Affymetrix microarrays analyzed (22,238 probe sets of 12,490 genes)
  - 78 the 3 SERMs and the 18 antipsychotics
  - 495 for the other 445 compounds
  - 135 for vehicle controls

Data Analysis

- For each drug treatment-vehicle pair all probe sets were ranked by amplitude (A)
  A= (t-v)/[(t+v)/2] ; t = treatment instance; v = vehicle instance
- Drug group profiles created with the Weighted Influence Model, Rank of Ranks (WIMRR) method
- A gene-set enrichment metric based on the Kolmogorov-Smirnov (KS) statistic was used where, for a given set of probes, the KS score gives a measure of how up (positive) or down (negative) the set of probes occurs within the profile of another treatment instance

Results

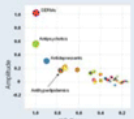
- We have identified a common effect of antipsychotics (both typical and atypicals) on the biosynthesis and regulation of fatty acids and cholesterol. 19 of the first 20 (95%) ranked probe sets in the antipsychotic group profile correspond to 13 genes involved in fatty acids and cholesterol biosynthesis, or in phospholipid metabolism (Table 1). For more details see poster NR7-009
- By comparing gene expression group profiles of all drug classes, it was further discovered that the group of SERMs affected lipid homeostasis in a manner similar to antipsychotics (KS scores of 0.997 and 0.806 for the top 20 and 100 probe sets, respectively) (Table 1 and Figure 2)

Table 1. Similar Molecular Signature of Antipsychotics and Selective Estrogen Receptor Modulators[1]

Gene	Description	Probe set	Rank: Antipsychotics	Rank: SERMs
*ACAT2**	acetyl-Coenzyme A acetyltransferase 2	209608_s_at	11	24
CYP51A1	cytochrome P450, family 51, subfamily A, polypeptide 1	219607_s_at	13	20
*DHCR7**	7-dehydrocholesterol reductase	201790_s_at	15	14
		201791_s_at	22	10
EBP	emopamil binding protein (sterol isomerase)	202735_at	20	33
FADS1	fatty acid desaturase 1	209982_s_at	18	31
		208964_s_at	7	39
FADS2	fatty acid desaturase 2	202218_s_at	5	19
*FASN**	fatty acid synthase	212218_s_at	14	11
FDFT1	farnesyl-diphosphate farnesyltransferase 1	210950_s_at	12	12
*FDPS**	farnesyl diphosphate synthase	201275_at	8	9
IDI1	isopentenyl-diphosphate delta isomerase 1	204615_s_at	45	17
		201625_s_at	9	2
*INSIG1**	insulin induced gene 1	201626_at	31	3
		201627_s_at	1	15
*LDLR**	low density lipoprotein receptor	202067_s_at	6	27
		202068_s_at	10	4
		211773_s_at	60	8
LSS	lanosterol synthase	202245_at	28	16
		211518_s_at	451	18
MVD	mevalonate (diphospho) decarboxylase	203027_s_at	253	13
PCYT2	phosphate cytidylyltransferase 2, ethanolamine	208577_at	19	79
RAB3II	RAB3II, member RAS oncogene family	219562_at	16	61
		203801_s_at	2	1
		208932_s_at	3	7
*SCD**	stearoyl-CoA desaturase (delta-9-desaturase)	211162_s_at	4	5
		211736_s_at	21	6
TM7SF2	transmembrane 7 superfamily member 2	210130_s_at	17	43

[1] The top 20 probe sets of both profiles of the antipsychotics and of the SERMs are listed.
* Genes of SREBP responsive mediated signaling pathway.

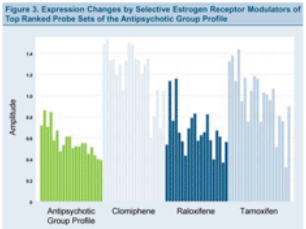
Figure 2. Selective Estrogen Receptor Modulators Affect Lipid Homeostasis in a Manner Similar to Antipsychotics



The amplitude of the 20 probe sets from the antipsychotic signature is represented by a dot for each group of drugs. The size of each dot corresponds to the absolute similarity score (KS value) of these 20 probe sets. Only groups of >5 drugs from a therapeutic class or subclass are represented here.

- The 3 SERMs profiled up-regulated the 20 probe sets at the top of the antipsychotic group profile (Figure 3)

Figure 3. Expression Changes by Selective Estrogen Receptor Modulators of Top Ranked Probe Sets of the Antipsychotic Group Profile



Change in expression between drug treatment and vehicle control is shown by the mean amplitude (Y axis) for each the top 20 ranked probe sets (left to right on the X axis, ordered by rank). The mean amplitude graphed is the average amplitude across replicates.

- The group profile of antipsychotics shares 58% of the top 100 probe sets of the SERM group profile, corresponding to 37 different genes
- Most of the genes up-regulated in common by both groups of antipsychotics and SERMs belong to the biological pathways of fatty acid and cholesterol biosynthesis (Figure 4)

Figure 4. Effect of Antipsychotics on the Biosynthesis of Fatty Acids and Cholesterol

Pathways of fatty acid and cholesterol biosynthesis are shown with major metabolite intermediates and enzymatic reactions (arrows). Genes coding for relevant enzymes, regulators, or transporters are shown with an asterisk: red for probe sets in the top 100 of both antipsychotic and SERM group profiles, blue in the antipsychotic group profile alone.

Discussion

- The common effect of antipsychotics and SERMs on genes involved in fatty acids metabolism and cholesterol biosynthesis appears to be specific and strong, as it covers most of all known genes of these biological pathways including a number of Sterol Regulatory Element Binding Proteins responsive genes. This effect was consistent across the various compounds of these 2 classes of drugs
- This novel observation points to:
  1. a potential implication of the estrogen pathway in the antipsychotic efficacy response
  2. the potential therapeutic benefit of SERMs for patients affected with schizophrenia or other mental illnesses
- These results are in agreement with:
  - the idea that estrogen plays a role in the etiology and/or the severity of schizophrenia symptoms
    - *ESR1* variants which may contribute to the risk of developing schizophrenia have been identified[3]
    - possible protective effect of estrogen: delayed age of onset in women, with a second onset peak after age 44 years[1]
    - symptoms vary with the menstrual cycle, worsening during phases of low estrogen[1]
  - the results of several clinical studies which have indicated a potential benefit of various SERMs for treating symptoms of common mental disorders, including mania and psychosis in schizophrenia patients[4-7]

Conclusion

- These results give news insights into the mechanism of action of antipsychotics and SERMs and for the first time demonstrate a common effect of these drugs on genes involved in lipid homeostasis
- Our findings suggest a potential antipsychotic effect of SERMs, which is consistent with several clinical studies that have shown that tamoxifen can reduce mania symptoms, and that raloxifene could improve symptoms of psychosis and cognitive functioning
- Further studies should be conducted to understand whether and how these molecular changes alter the fluidity of cell membranes of neurons and impact on neuronal connectivity
- Additional larger clinical studies are needed to better evaluate the potential therapeutic benefit of SERMs for patients affected with schizophrenia or other mental illnesses

References

1. Grigoriadis,S. and Seeman,M.V., 2002. Can J Psychiatry. 47, 437-442.
2. Power,R.F et al. 1991. Science. 254, 1636-1639.
3. Weickert,C.S et al. 2008. Hum Mol Genet. 17, 2293-2309.
4. Kulkarni,J et al. 2006. Psychoneuroendocrinology. 31, 543-547.
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Presented at the 162nd Annual Meeting of the American Psychiatric Association
May 16-21, 2009 San Francisco, CA

NR1-026 The Comparative Efficacy of Iloperidone and Haloperidol Across Four Short-Term Controlled Trials

John Feeney, MD; Curt Wolfgang, PhD; Mihael Polymeropoulos, MD; Paolo Baroldi, MD, PhD; Jennifer Hamilton, MS.
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Abstract

Objective: The performance of iloperidone, a new atypical antipsychotic, relative to haloperidol in the treatment of schizophrenia was examined across 4 short-term controlled trials.

Methods: Placebo-controlled trials (PCTs) conducted to support registration often include a positive control as an internal measure of assay sensitivity. In a 5-week PCT conducted with iloperidone, haloperidol served as the active control. Because the validity and reliability of active comparisons in PCTs has been questioned, other sources of comparative data were also examined. Three active-controlled trials (ACTs) were conducted comparing iloperidone and haloperidol. While data from these trials were intended to be pooled and formally compared to show non-inferiority with long-term treatment, the short-term (6 week) data from these 3 trials provide another source of information bearing on the relative short-term efficacy.

Results: In the PCT, the change from baseline on the PANSS-T differed by 4 points between the iloperidone group and the haloperidol group (intent-to-treat, last-observation-carried-forward (LOCF) analysis). In all 3 ACTs, the effect sizes were numerically similar for iloperidone (mean dose 12 mg/day) and haloperidol (mean dose 12 mg/day), with differences of 0.4, 0.7, and 1.7 points. The dropout rate in the PCT (63%) was twice that observed in each of the 3 ACTs (14-29%). This difference in retention rates between short-term PCTs and ACTs in schizophrenia/schizoaffective patients has been previously observed.

Conclusions: Because higher dropout rates force more assumptions about missing data in LOCF analyses, lower dropout rates in the ACTs may allow for a more valid and reliable comparison between drugs. In these perhaps more reproducible and clinically meaningful comparisons, similar effect sizes were observed for iloperidone 12 mg/day and haloperidol 12 mg/day in the treatment of the symptoms of schizophrenia. Vanda Pharmaceuticals sponsored this analysis.

Introduction

- Iloperidone, a mixed D2/5-HT2 receptor antagonist, is a new atypical antipsychotic
- Clinicians understandably want to know how the efficacy of a new drug product compares to the efficacy of older established drug products
- Recent actions by Congress, HHS, and FDA suggest increasing interest in comparative efficacy data
- Before making generalizations about comparative efficacy based on results from clinical trials, factors that may influence the results of clinical trials needs to be investigated
- Assay Sensitivity
  - A large percentage (25 %) of placebo-controlled trials of effective drugs for schizophrenia fail to demonstrate a difference between the drug and placebo (1)
  - Therefore, in trials of new drugs, an active control group is often included in the trial design to determine assay sensitivity
  - If the new drug fails to separate from placebo, the performance of the positive control helps determine whether the new drug truly failed or whether the study was incapable of showing a difference (poor assay sensitivity)
- Previously published work demonstrates that dropout rates from the active treatment arms in short-term trials in schizophrenia are systematically greater in trials that include a placebo arm (2)

Methods

- The comparative efficacy of iloperidone (12 mg/day) and haloperidol (15 mg/day) was investigated across 4 phase III short-term controlled trials: 1 placebo-controlled trial (PCT) and 3 active-controlled trials (ACTs)
- **Study 3000**
  - Six-week, randomized, double-blind, PCT; US centers
  - Five randomized groups: Placebo (N=127), iloperidone 4 mg/day (N=121), iloperidone 8 mg/day (N=125), iloperidone 12 mg/day (N=124), and haloperidol 15 mg/day (N=124) to provide assay sensitivity
  - Only the iloperidone 12 mg/day and the haloperidol 15 mg/day groups were considered for this comparative efficacy evaluation
- **Study 3001**
  - Six-week, randomized, double-blind, haloperidol-ACT; European centers
  - Iloperidone 4-16 mg/day, mean dose of 11.4 mg/day at week 6, (N=454), haloperidol 5-20 mg/day, mean dose of 11.9 mg/day at week 6, (N=146)
- **Study 3002**
  - Six-week, randomized, double-blind, haloperidol-ACT; Asian Pacific centers
  - Iloperidone 4-16 mg/day, mean dose of 12.9 mg/day at week 6, (N=420), haloperidol 5-20 mg/day, mean dose of 14.0 mg/day at week 6, (N=137)
- **Study 3003**
  - Six-week, randomized, double-blind, haloperidol-ACT; Mexican and Southern American centers
  - Iloperidone 4-16 mg/day, mean dose of 13.3 mg/day at week 6, (N=365), haloperidol 5-20 mg/day, mean dose of 14.5 mg/day at week 6, (N=122)

Main Inclusion Criteria

- Male and non-pregnant female patients ages 18-65
- Diagnosis of schizophrenia or schizoaffective disorder according to DSM-IV
- Positive and Negative Syndrome Scale Total (PANSS-T) ≥ 60

Comparative Efficacy Evaluation

- Post hoc comparisons of iloperidone- and haloperidol-treated patients
- Not designed for statistical inference
- Outcome Measure for Comparisons: Mean change from baseline at Week 6 in PANSS-T score, Last Observation Carried Forward (LOCF)

Results

Patient Demographics

- Baseline demographics of iloperidone-, haloperidol-, and placebo-treated patients were similar across all studies (Table 1)

Table 1. Baseline Demographic and Background Characteristics of the Analysis Populations for Studies 3000, 3001, 3002, and 3003

Characteristics	Study 3000 N=621	Study 3001 N=600	Study 3002 N=557	Study 3003 N=487
Age, years				
Mean (SD)	38.8 (9.7)	37.3 (11.8)	33.7 (9.6)	36.1 (10.8)
Range	18 - 68	18 - 68	18 - 64	18 - 65
Gender, n (%)				
Male	442 (71)	339 (57)	347 (62)	310 (64)
Female	179 (29)	261 (44)	210 (38)	177 (36)
Race, n (%)				
White	295 (48)	591 (99)	2 (< 1)	315 (65)
Black	263 (42)	1 (< 1)	1(< 1)	20 (4)
Asian	8 (1)	2 (< 1)	465 (83)	2 (< 1)
Other	55 (9)	6 (1)	89 (16)	150 (31)
Mean Weight (SD), kg	86.7 (20.6)	74.2 (14.6)	57.7 (12)	70.2 (14.7)
Age of diagnosis, years				
Mean (SD)	23.2 (8.0)	25.3 (8.6)	24 (7.1)	22.7 (8.7)
Median (range)	21 (3 - 57)	23 (0 - 67)	23 (11 - 57)	21 (10 - 61)
Mean PANSS-T (SD)	95.4 (15.9)	89.4 (16.9)	90.5 (20.7)	92.8 (21)
DSM-IV classification of schizophrenia, n (%)				
Disorganized	13 (2)	43 (7)	83 (15)	35 (7)
Catatonic	0	6 (1)	9 (2)	11 (2)
Paranoid	344 (55)	389 (65)	255 (46)	322 (66)
Residual	2 (< 1)	73 (12)	45 (8)	53 (11)
Undifferentiated	68 (11)	49 (7)	29 (5)	52 (11)
Schizoaffective	193 (31)	48 (8)	136 (24)	14 (3)
Missing	1(< 1)	1 (< 1)	0	0

Supported by funding from Vanda Pharmaceuticals Inc.

Historical Dropout Rates Observed in PCTs and ACTs

- Kemmler et. al. 2005 reviewed 31 trials
  - 11 PCTs and 20 ACTs
  - Total sample size = 10,058 subjects (42- 1,996 patients/trial)
  - Trial duration = 4-12 weeks
- Table 2 shows that the attrition rates observed for active arms in PCTs are substantially higher than those in ACTs
- The difference in mean attrition rate in the active treatment arms between PCTs and ACTs was about 20 percentage points
- Furthermore, considering only the dropouts due to lack of efficacy, the rates in the active treatment arms were significantly higher (~ 15 percentage points) in PCTs than in ACTs (data not shown)
- Dropout rates for reasons other than lack of efficacy were similar between the active treatments of PCTs and ACTs (data not shown)

Table 2. Comparison of Dropout Rates in Active Treatment Arms of PCTs and ACTs

Type of Active Treatment	Mean Dropout Rate, % PCTs	ACTs	Odds Ration (95% CI) PCT vs ACT	Statistics (p value)
Second-Generation Antipsychotics	48	28	2.34 (1.58-3.47)	p<0.001
Classical Antipsychotics	55	37	2.10 (1.29-3.40)	p = 0.005
All Antipsychotics	49	30	2.20 (1.46-3.33)	p<0.001

* Adapted from Kemmler et al. 2005

- Kemmler's hypothesis to explain different dropout rates:
  - Health care providers may have an increased readiness during PCTs vs. ACTs to discontinue a patient early for lack of efficacy because they know one of the possible treatments (placebo) is ineffective
  - Patients may be less willing to wait for signs of improvement in a PCT vs. ACT knowing that one of the possible treatments (placebo) is ineffective
- Table 3 shows that dropout rates are more common in the placebo arms than in the active treatment arms in PCTs
- The difference in mean attrition rate in the placebo arm and the active treatment arm was about 10 percentage points
- The difference in dropout rate in the active treatment group between PCTs and ACTs was considerably larger that those seen between placebo and active treatment within PCTs

Table 3. Comparison of Dropout Rates in Placebo Arms and Active Treatment Arms in PCTs

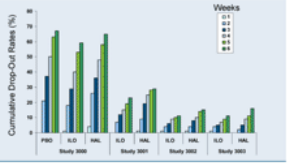
Type of Active Treatment	Mean Dropout Rate, % PBO	Active Treatment	Odds Ratio (95% CI) PCT vs ACT	Statistics (p value)
Second-Generation Antipsychotics	60	48	1.63 (1.37-1.94)	p<0.001
Classical Antipsychotics	63	55	1.39 (1.14-1.69)	p = 0.01
All Antipsychotics	60	49	1.58 (1.36-1.84)	p<0.001

* Adapted from Kemmler et al. 2005

Dropout Rates Observed Across Four Iloperidone Studies

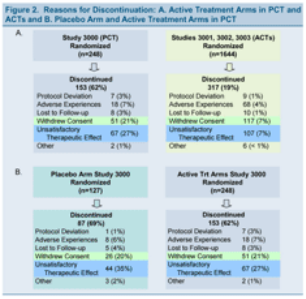
- The cumulative dropout rates, per week, during the initial 6-weeks double-blind phase of studies 3000, 3001, 3002, and 3003 are shown in Figure 1

Figure 1. Cumulative Dropout Rates by Week for PCT and ACTs of Iloperidone



- The dropout rates in the active treatment arms of the PCT were significantly higher than the dropout rates in the ACTs throughout the whole 6-weeks (Figure 1)
- By the end of the 6-week double-blind portion of the study, the dropout rates for the active treatment arms were 62% for the PCT and 19% for the ACTs (Figure 2A)
- Within the PCT, the dropout rate in the placebo arm was higher (69%) than the drop-out rate in the combined iloperidone and haloperidol arms (62%) (Figure 2B)
- The most common reasons for discontinuation in all studies were unsatisfactory therapeutic effect and withdrawal of informed consent
- The dropout rate due to unsatisfactory therapeutic effect and withdrawal of informed consent in the active treatment arms were much higher in the PCT (27% and 21%, respectively) than in the ACTs (7% and 7%, respectively) (Figure 2A)
- The dropout rates were consistent across all other reasons for discontinuation

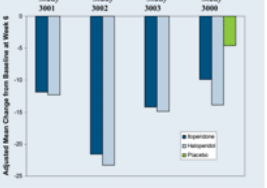
Figure 2. Reasons for Discontinuation: A. Active Treatment Arms in PCT and ACTs and B. Placebo Arm and Active Treatment Arms in PCT



PANSS-Total Scores

- In the ACTs, Studies 3001, 3002, and 3003, the change-from-baseline PANSS-T scores for the iloperidone and haloperidol groups differed by 0.4, 1.7, and 0.7 respectively (Figure 3)
- In the PCT, Study 3000, the change-from-baseline PANSS-T scores for the iloperidone and haloperidol groups differed by 4 points (LOCF: p<0.4)

Figure 3. PANSS Total Score: Mean Change from Baseline at Week 6, LOCF Analysis of Studies 3000, 3001, 3002, and 3003



Conclusion

- The dropout patterns across Studies 3000, 3001, 3002, and 3003 are consistent with the previous observation that trials that include a placebo arm have higher dropout rates in all randomized groups
- As suggested by Kemmler et al, investigators and patients may both have an increased readiness to stop treatment earlier during PCTs vs. ACTs because they know one of the possible treatments (placebo) is ineffective
- The lower dropout rates in the ACTs that included iloperidone and haloperidol treatment arms necessitate fewer assumptions about outcome and might therefore provide more reliable and valid estimates of comparative efficacy than the PCT
- Iloperidone at a dose of 12 mg/day provides comparable efficacy to haloperidol 15 mg/day

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NR1-058

Effect of Polymorphisms in the Dopamine Receptor 2 Gene on Iloperidone Efficacy for the Treatment of Patients With Schizophrenia

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Abstract

Objective: It has been proposed that single nucleotide polymorphisms (SNPs) in the dopamine receptor 2 gene (*DRD2*) play a role in the presentation of schizophrenia symptoms and their treatment, and may explain some inter-individual differences observed in antipsychotic response. Iloperidone is a novel mixed D2/5-HT2 antagonist with high affinity for DRD2. In clinical trials, iloperidone has demonstrated efficacy for a broad range of schizophrenia symptoms, with a favorable profile on key metabolic parameters and on movement disorders (extrapyramidal symptoms and akathisia). A pharmacogenetic analysis of *DRD2* was conducted in a phase III clinical trial to identify DNA polymorphisms predictive of iloperidone response.

Method: A mixed-effects model repeated measures analysis was performed by genotype, for several *DRD2* SNPs, on improvement of symptoms assessed by the Positive and Negative Syndrome Scale Total (PANSS-T) score.

Results: SNP allele frequencies varied across populations. Genotype differences were statistically significant between Blacks, Whites and Asians. In the overall population, and in Whites alone, one SNP (Taq1A, rs1800497), located in the 3' region of *DRD2*, was significantly associated (p≤0.05) with iloperidone efficacy at days 7, 10, 14 and 21, but not at day 28. The same trend was observed in Blacks, but did not reach statistical significance.

Conclusions: These results suggest that rs1800497 may contribute to the early inter-individual differences in the therapeutic efficacy of iloperidone. To explain these findings, the functional effect of rs1800497 on the expression and/or function of *DRD2* remains to be investigated. This study provides new insights into the response to iloperidone, developed with the ultimate goal of directing therapy to patients with the highest benefit-to-risk ratio. Vanda Pharmaceuticals sponsored this study.

Introduction

- It has been proposed that polymorphisms in the *DRD2* gene play a role in the etiology of schizophrenia symptoms and their treatment
- Several *DRD2* polymorphisms affect the binding affinity of neuroleptics[1,2], supporting the idea that they may explain some of the inter-individual differences observed in response to treatment[3-6]
- Iloperidone is a novel mixed D2/5-HT2 antagonist with high affinity for the dopamine D2 receptor[7,8]
- We have previously reported the discovery, in a whole genome association study (WGAS), of 6 genetic markers associated with iloperidone efficacy in a phase III clinical trial[9]
- The aim of the present study was to further understand inter-individual differences of iloperidone efficacy by analyzing various common *DRD2* polymorphisms previously associated with response to other antipsychotics but not available on the microarray platform used for the WGAS
- Several single nucleotide polymorphisms (SNPs) in the *DRD2* gene are expected to have functional significance, and have been analyzed for possible association with the risk of developing schizophrenia and with the response to antipsychotic medications (Table 1 & Figure 1)
- In the study reported here, the possible effects of the -241A/G, -141C Ins/Del, His313His, Taq1A, rs2283265 and rs1076560 polymorphisms were evaluated in 409 patients who participated in a phase III clinical trial which assessed the efficacy of iloperidone as measured by changes in the Positive and Negative Syndrome Scale Total (PANSS-T)

Supported by funding from Vanda Pharmaceuticals Inc.

Table 1. *DRD2* Polymorphisms Analyzed

Polymorphism		Location	Comment
rs1799978	-241A/G	Upstream	Believed to regulate *DRD2* expression levels and striatal receptor density[10,11] Chinese patients treated with risperidone who carried the -241A allele showed a greater response than those who had the G allele[12]
rs1799732	-141C Ins/Del	Upstream	Believed to regulate *DRD2* expression levels and striatal receptor density[10,11] Schizophrenia patients who carry the -141C Del allele took a significant longer time to respond to antipsychotics (either risperidone, olanzapine or chlorpromazine) than those who carry the -141C Ins allele[3,12,13]
rs2283265 rs1076560		Intron 5 Intron 6	Alternative splicing of exon 6 yields at least 3 isoforms: short (DRD2S), long (DRD2L) and longer. These two SNPs decrease the expression of *DRD2S*, which is mainly expressed presynaptically, relative to the *DRD2L* isoform predominantly expressed postsynaptically[14]
rs6275	His313His	Exon 7	Patients treated with either clozapine, haloperidol or risperidone carrying the C/C genotype were reported to have higher mean improvement scores than patients who had an alternative genotype[5]
rs1800497	TaqA	Downstream	This polymorphism originally assigned to *DRD2* was recently shown to be located within exon 8 of *ANKK1*. It is a missense mutation (Lys713Glu) A1 allele has been linked to low striatal dopamine D2 receptor density in healthy individuals[10,11] A1 allele may be associated with increased activity of the striatal L-amino acid decarboxylase, the final enzyme in the biosynthesis of dopamine[15] A2 allele has been associated with schizophrenia in French and Russian populations[3,16,17] South Indian patients carrying the A2/A2 genotype were reported to have a significantly higher antipsychotic response than A1/A2 heterozygotes[6] In a Caucasian population, the A1 allele was shown to be in linkage disequilibrium with the minor allele of rs2283265 and rs1076560 associated with *DRD2* splicing isoforms[14]

Methods

Clinical Trial

- This 4-week, randomized, double-blind, placebo- and ziprasidone-controlled, multicenter inpatient phase III trial evaluated efficacy, safety, and tolerability of iloperidone in patients with an acute exacerbation of schizophrenia. The design, conduct, and overall results of the clinical study have been previously reported[18]

Treatment

- Random assignment (2:1:1)
  - Iloperidone 24 mg/d (12 mg bid); N=218
  - Ziprasidone 160 mg/d (80 mg bid); N=103
  - Placebo; N=105

Efficacy

- Measured by the change from baseline in the PANSS-T score

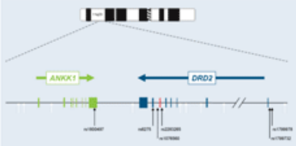
Analysis

- Genotype assays were performed as previously reported[9,19,20]
- Hardy-Weinberg equilibrium (HWE) analysis was performed using Haploview 4.1[21]
- A mixed-effects model repeated measures analysis was performed by genotype on improvement of symptoms assessed by the PANSS-T score

Results

- The allele frequencies of the *DRD2* SNPs were found to vary across populations (Table 2), as reported in other studies (http://www.ncbi.nlm.nih.gov/SNP)
- For -141C Ins/Del and His313His, genotype differences were statistically significant between Blacks, Whites and Asians (Fisher's exact test, $p = 10^{-18}$, $p = 5.3 \times 10^{-12}$ respectively). However, no significant deviation from Hardy-Weinberg equilibrium was observed within either population
- The genotype distribution of rs2283265, and rs1076560 was statistically different between Blacks and Whites ($p = 5.5 \times 10^{-7}$, $p = 3.6 \times 10^{-7}$ respectively)
- As previously reported in Caucasians[15], the Taq1A polymorphism (rs1800497) and the 2 intronic SNPs (rs2283265 and rs1076560) were in strong LD in both the Black and White populations (D'=1, LOD>2)

Figure 1. Genome View of the *DRD2* Gene and Associated SNPs



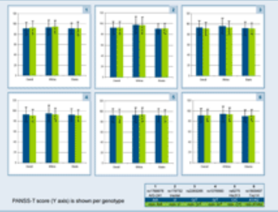
Vertical bars represent exons. The red bar shows the alternatively spliced exon 6 of *DRD2*. The white arrows show the location of SNPs previously typed in a whole genome association study. The black arrows points to the location of the SNPs analyzed in the study presented here.
Rs1800497 originally assigned to *DRD2* was later shown to be located within *ANKK1*.

Table 2. Allele and Genotype Frequencies

Polymorphism		Race	Minor Allele Frequency (%)	Genotype Frequency (%)		
				G/G	A/G	A/A
rs1799978	-241A/G	all	10.5	1.3	18.4	80.3
		Black	12.1	2.0	20.2	77.8
		White	9.9	0.7	18.4	80.9
		Asian	7.6	0.0	15.2	84.8
				D/D	D/I	I/I
rs1799732	-141C Ins/Del	all	32.1	13.9	36.4	49.7
		Black	48.4	24.2	48.5	27.3
		White	13.7	2.8	21.8	75.4
		Asian	22.1	5.9	32.3	61.8
				T/T	G/T	G/G
rs2283265		all	16.3	4.0	24.5	71.5
		Black	9.4	1.0	16.7	82.3
		White	21.5	7.6	27.8	64.6
		Asian	31.8	6.1	51.5	42.4
				A/A	A/C	C/C
rs1076560		all	16.3	4	24.6	71.4
		Black	9.4	1	16.7	82.3
		White	21	7.6	26.9	65.5
		Asian	32.4	5.9	52.9	41.2
				C/C	C/T	T/T
rs6275	His313His	all	50.0	27.8	44.4	27.8
		Black	63.5	13.0	47.1	39.9
		White	34.7	44.9	40.8	14.3
		Asian	38.6	37.1	48.6	14.3
				A1/A1	A1/A2	A2/A2
rs1800497	Taq1A	all	29.5	10.9	37.1	52.0
		Black	31.0	11.8	38.4	49.8
		White	26.6	10.4	32.4	57.2
		Asian	33.8	11.8	44.1	44.1

- None of these SNPs was associated with baseline PANSS-T in the overall study population or within either the Black or the White population (Figure 2)

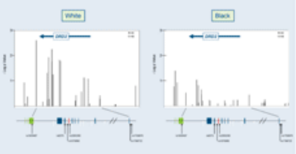
Figure 2. Baseline PANSS-T Score and *DRD2* Genotypes



PANSS-T score (Y axis) is shown per genotype

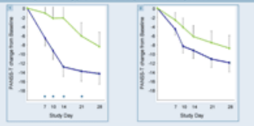
- The genotype effect of the *DRD2* SNPs on iloperidone efficacy was evaluated overall and separately in the Black and the White populations
- The highest signal was detected in the 3' region of the *DRD2* gene, with the lowest p value obtained with the Taq1A polymorphism in the Whites at day 14 (Figure 3)
- A statistical significant effect was observed at days 7, 10, 14 and 21 (Figure 4); the largest difference was detected between the two Taq1A genotype classes at day 14, with a mean change in PANSS-T of -12.7 (±2.1) for non-A1/A2 patients treated with iloperidone versus -2.1 (±2.7) for patients who carry the A1/A2 genotype (p=0.003)
- A numerical difference remained between the two genotype groups at day 28 in Whites (Figure 4A), and was also observed in Blacks across the entire trial (Figure 4B), but without reaching statistical significance
- Both intronic SNPs were also significantly associated with iloperidone response in the White population at day 14 (p=0.01 and p=0.05 for rs2283265 and rs1076560 respectively). Whites carrying the non-G/T genotype for rs2283265 experienced higher efficacy (PANSS-T with mean change of −11.8 (±2.0) than patients with the G/T genotype, −2.4 (±3.0); p=0.01

Figure 3. Genotype Effect of *DRD2* SNPs on Iloperidone Efficacy at Day 14



P values (vertical axis) from the MMRM analysis of change in PANSS-T are shown for the genomic region containing the *DRD2* gene in order of the SNPs' physical locations (horizontal axis), in the White and Black populations separately

Figure 4. Taq1A Genotype Effect on Iloperidone Response



Effect of the Taq1A polymorphism on iloperidone response is shown for the white (1) and black (2) populations, per genotype group (A1/A2 in green, non-A1/A2 in blue). * p<0.05.

Discussion

- The Taq1A polymorphism (rs1800497) was shown to be associated with iloperidone efficacy. The strongest statistical significance was obtained at day 14, while the 6 genetic markers previously discovered showed the strongest association with iloperidone response at day 28
- Analysis of the combination of all these markers may clarify if the Taq1A polymorphism has an additive predictive value, or if it is a distinct marker of early response
- At this time, it is still unknown whether this Taq1A polymorphism affects the function of the dopamine receptor D2 or the protein encoded by ANKK1, and how it influences antipsychotic response
- In our study, this genetic marker did not appear to differentiate patients for their response to ziprasidone. It is possible that the limited number of patients treated with ziprasidone was not sufficient to reach statistical significance between genotypes

Conclusion

- These results suggest that the *DRD2* Taq1A polymorphism (rs1800497) may contribute to the early inter-individual differences in the therapeutic efficacy of iloperidone
- The functional effect of rs1800497 on the expression and/or function of *DRD2* remains to be investigated, and additional pharmacogenomic studies should be conducted to confirm the clinical value and the predictive application of this finding
- This study provides new insights into the response to iloperidone, developed with the ultimate goal of directing therapy to patients with the highest benefit-to-risk ratio

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NR1-033 Efficacy of Iloperidone is Comparable to Risperidone in Analyses of a Placebo- and Risperidone-Controlled Clinical Trial for Schizophrenia

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Abstract

Objective: In trials to establish the efficacy of antipsychotics, patients are prone to drop out early if they experience unsatisfactory results in the initial days of the study. Although statisticians generally acknowledge that results from LOCF are biased, its use in regulatory settings has persisted for various reasons. As an alternative to LOCF, we implemented a simplified pattern mixture model approach to examine the efficacy of iloperidone and risperidone in a placebo-controlled Phase 3 study.

Methods: The efficacy of iloperidone at a dose range of 12-24 mg/d was evaluated in a 6-week, double-blind, placebo- and active-controlled (risperidone 6-8 mg/d) trial of acute exacerbation of schizophrenia. Dropout cohort data was analyzed to determine what effect dropouts had on efficacy measures. Based on the longer titration period for iloperidone, an analysis was conducted implementing length of stay into the model and a subgroup analysis using LOCF of patients that received ≥14 days of treatment.

Results: The length of stay covariate was significant (p<0.001) and when adjusting for length of stay, both dose groups of iloperidone, 12-16 mg/d and 20-24 mg/d showed significantly greater improvement than placebo on the PANSS-T (-12.6; p=0.021 and -15.4; p=0.001, respectively) and BRPS (-8.1; p=0.018 and -9.4; p=0.001, respectively) and both iloperidone treatments are similar to risperidone on PANSS-T (-15.6; p=<0.001) and BPRS (-9.6; p=0.001). An LOCF analysis of patients with ≥14 days of treatment confirms the comparable efficacy of iloperidone to risperidone, supported from the overlapping 95% confidence intervals and by the observed cases data at Week 6.

Conclusion: In this Phase 3 schizophrenia trial, an analysis which adjusts for drug titration differences, showed that iloperidone was more effective than placebo and comparable to risperidone for the treatment of acute psychotic exacerbation.
Vanda Pharmaceuticals sponsored this study.

Introduction

- Iloperidone (ILO), a mixed $D_2/5\text{-}HT_2$ antagonist, is a novel antipsychotic medication approved by the Food and Drug Administration (FDA) for the acute treatment of adults with schizophrenia
- The majority of Phase III clinical trials for antipsychotics are run as placebo-controlled trials including an active control for assay sensitivity
- When an active comparator is being used for assay sensitivity, titration schedules between the drug being studied and the active comparator can lead to a bias in efficacy measures
- The bias may result because patients are prone to drop out early if they experience unsatisfactory results in the initial days of the study which have an impact on Last Observation Carried Forward (LOCF) analysis
- Although statisticians generally acknowledge that LOCF has the potential to introduce bias, its use in regulatory settings has persisted for various reasons
- Instead of using LOCF, we implemented alternative approaches such as: (1) using length of stay in the study and (2) looking at patients who received ≥ 14 days of treatment to examine the efficacy of iloperidone and risperidone[2]
- These approaches allow for the comparison of drug effects in patients with similar lengths of stay in the study or who reach steady-state drug levels at different times

Supported by funding from Vanda Pharmaceuticals Inc.

Methods

- Phase III, randomized, double-blind, placebo- and risperidone (RIS)-controlled trial conducted at 32 centers in the US and 35 non-US centers[1]
- Inpatients were randomized to one of four treatment arms: iloperidone (12-16 mg/d), iloperidone (20-24 mg/d), risperidone (6-8 mg/d) and placebo
- Randomization and titration schedules are shown in Table 1

Patients main inclusion criteria

- Men or woman aged 18 to 65 years
- DSM-IV diagnosis of schizophrenia or schizoaffective disorder and need for psychiatric treatment
- Baseline Positive and Negative Syndrome Scale Total (PANSS-T) score ≥ 60
- Baseline PANSS positive (PANSS-P) ratings ≥ 4 for 3 or more of the following items: delusions, conceptual disorganization, hallucinatory behavior, grandiosity, and suspiciousness/persecution

Patients main exclusion criteria

- Primary psychiatric diagnosis (Axis I) or comorbid diagnosis (Axis II), other than schizophrenia
- Diagnosis of a substance abuse disorder
- Patients with psychotic symptoms failing to improve following sufficient exposure to a therapeutic dose of any antipsychotic treatment for the prior 2 years

Statistics

- Efficacy analyses were based on the intent-to-treat population, comprising all patients receiving ≥ 1 dose of study medication with ≥ 1 complete PANSS assessment using LOCF method with the following adaptations
  - All patients by drop-out cohorts
  - All patients with length of stay as a covariate
  - Only patients who received ≥ 14 days of treatment

Table 1. Randomization and Titration Schedules

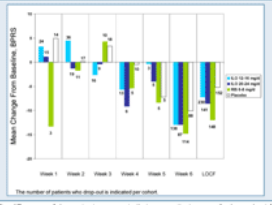
Pre-randomization phase		Short-term double-blind phase (bid dosing)		
Day -30 to -3	Day -2 to 0[a]	Day 1 to 7		Day 8 to 42
Screening	Single blind placebo run-in period (bid dosing)	Fixed titration period (mg/d)		Flexible maintenance period (mg/d)
	Placebo	Ilo low: 2→4→8→12 Ilo high: 2→4→8→12→16→20 Pbo Ris: 2→4→6		Ilo low: 12[b] or 16 Ilo high: 20[b] or 24 Pbo Ris: 6[b] or 8

Ilo=iloperidone; Ris=risperidone; Pbo=placebo
[a]Placebo run-in period lasted a minimum of 3 days; the last day of placebo run-in Period was baseline (Day 0)
[b]Titration target dose

Results

- Because of the 1-week titration of iloperidone and the 3-4 additional days of treatment needed to achieve steady-state exposures (~17-hr half-life), it is not surprising to observe that patients treated with iloperidone do not have the opportunity to experience a full therapeutic effect until receiving ~14 days of treatment as observed when looking at the mean change from baseline for BPRS drop-out cohorts as shown in Figure 1

Figure 1. Mean Change from Baseline, BPRS by Drop-out Cohorts



The number of patients who drop-out is indicated per cohort

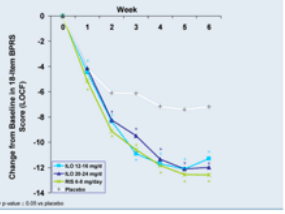
- The differences of drop-out rates suggests that more patients generally dropped out from the iloperidone and placebo arms as compared to the risperidone arms
- These drop-out rate differences were exacerbated in the first two weeks of the study
- As discussed, such unbalanced drop-out rates in both numbers and timing can potentially impact outcomes under some analyses, including the LOCF analysis
- The length of stay analysis attempts to account for the differences and inform the statistical model, when efficacy comparisons across drugs are performed (Table 2)

Table 2. Adjusted Mean Change on BPRS and PANSS-T

	Treatment	Adj Mean Change from Baseline at Week 6	Pairwise Comparisons (p-values) ILO 12-16 mg/d	ILO 20-24 mg/d	RIS 6-8 mg/d
BPRS	ILO 12-16 mg/d	-8.1		0.223	0.153
	ILO 20-24 mg/d	-9.2	0.223		0.854
	RIS 6-8 mg/d	-9.6	0.153	0.854	
	Placebo	-5.6	0.018	0.001	0.001
PANSS-T	ILO 12-16 mg/d	-12.6		0.121	0.098
	ILO 20-24 mg/d	-15.4	0.121		0.925
	RIS 6-8 mg/d	-15.6	0.098	0.925	
	Placebo	-8.6	0.021	0.001	<0.001

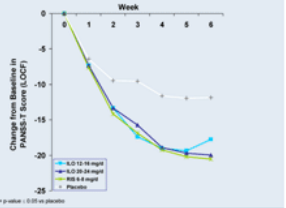
- The results (Table 2) demonstrate that the length of stay covariate is significant (p<0.001)
- When adjusting for length of stay (Table 2) , two key observations are made:
  - Iloperidone 12-16 mg and 20-24 mg doses are significantly superior to placebo
  - Both iloperidone treatments are similar to risperidone 6-8 mg
- Another method to look at how the drop-out of the first 2 weeks with iloperidone impacts the LOCF analysis is to only look at those patients that stayed in the study and achieved steady-state levels of iloperidone ≥ 14-days (Figures 2 & 3)

Figure 2. Patients Treated ≥ 14 Days - BPRS



* = p-value ≤ 0.05 vs placebo

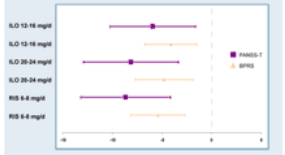
Figure 3. Patients Treated ≥ 14 Days – PANSS-T



* = p-value ≤ 0.05 vs placebo

- An LOCF analysis of patients with ≥14 days of treatment (75% of the patients) confirms the comparable efficacy of iloperidone to risperidone on both the BPRS and PANSS-T scores (Figures 2 & 3)

Figure 4. 95% Confidence Intervals



Placebo-Corrected Change from Baseline with 95% Confidence Intervals
+2 Week Population – Last observation carried forward, BPRS or PANSS-T Scores

- The comparable efficacy between iloperidone and risperidone is further supported by the overlapping 95% confidence intervals on both the BPRS and PANSS-T scores (Figure 4)

Conclusion

- The analysis of length of stay is a simplistic method where the timing and pattern of drop-outs is used as a covariate to inform and construct the statistical model
- The results demonstrate that the length of stay covariate is significant (p<0.001)
- When adjusting for length of stay, two key observations are made:
  - Iloperidone 12-16mg and 20-24 mg doses are significantly superior to placebo
  - Both iloperidone treatments are similar to risperidone 6-8 mg
- An LOCF analysis of patients with ≥14 days of treatment confirms the comparable efficacy of iloperidone to risperidone 12-16 mg/d and 20-24 mg/d doses to risperidone 6-8 mg/d
- This comparable efficacy is further supported the overlapping 95% confidence intervals

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NR1-095 Effect of 6 Genetic Makers Associated With Iloperidone Efficacy on Long Term Clinical Outcome of Patients Who Switch to Iloperidone

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Abstract

Objective: In a double-blind, placebo- and active-controlled phase III clinical trial, 6 single nucleotide polymorphisms (SNPs) were found to be associated with the efficacy of a novel antipsychotic, iloperidone, during the short-term phase of the study. Patients, who received iloperidone, ziprasidone or placebo for four weeks, were then enrolled in an optional open-label 6-month extension phase where they all received iloperidone. A pharmacogenetic analysis was conducted in the extension phase for the individuals who switched to iloperidone, in an attempt to validate the genotype effect of the 6 SNPs in this independent group of patients.

Method: Analysis of the genotype effect on iloperidone response, as measured by change in the Positive and Negative Syndrome Scale Total (PANSS-T) score, was performed using a general linear model with baseline value as a covariate. For patients who switched to iloperidone, PANSS-T was analyzed at the end of the study (day 203) as improvement from the baseline of the extension phase.

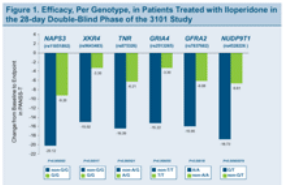
Results: A statistical significant association was observed between iloperidone efficacy and SNP rs4528226 genotypes for patients who switched from ziprasidone or placebo to iloperidone. Despite a relative small number of patients available, SNPs rs11851892, rs9643483, rs875326, and rs7837682 showed a similar trend without, however, reaching statistical significance. These results are consistent with the genotype effects observed for iloperidone-treated patients in the short-term phase of the clinical trial.

Conclusions: This study is a first step in validating the 6 iloperidone efficacy markers in an independent population. The findings reported here support the application of pharmacogenomics to differentiate medication options and improve individualized treatments for schizophrenia. Vanda Pharmaceuticals sponsored this study.

Introduction

- Iloperidone is a novel mixed D2/5-HT2 antagonist with high affinity for the dopamine D2 receptor. In clinical trials, iloperidone has demonstrated efficacy for a broad range of schizophrenia symptoms with a favorable profile on key metabolic parameters and movement disorders (extrapyramidal symptoms and akathisia)[1-4]
- We have previously reported the association of 6 single nucleotide polymorphisms with treatment response for patients affected with schizophrenia who received iloperidone in the 28 day double-blind period of a phase III clinical trial (Figure 1)[5]

Figure 1. Efficacy, Per Genotype, in Patients Treated with Iloperidone in the 28-day Double-Blind Phase of the 3101 Study

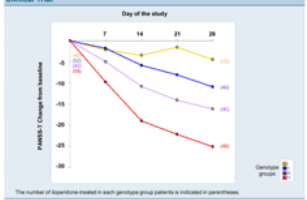


P values from the mixed-effects model repeated measures (MMRM) analysis are shown for each SNP.

Supported by funding from Vanda Pharmaceuticals Inc.

- We defined 4 groups of genotype combinations (groups I to IV) based on the number of predictive genotypes associated with enhanced response, and showed that the probability of response to iloperidone treatment increased with the number of favorable genotypes carried by a patient (Figure 2)[6]

Figure 2. Genotype Effect for Patients Treated with Iloperidone in a 28-Day Clinical Trial



The number of iloperidone-treated in each genotype group patients is indicated in parentheses.

- In an attempt to validate this finding in an independent group of patients, we analyzed the genotype effect of the 6 SNPs in patients treated with iloperidone in an optional open-label 6-month extension phase. These patients had previously received ziprasidone or placebo in the first 28 day double-blind period of the study (Figure 3)
- Despite the relative small number of patients who completed the 6-month extension period, the same genotype trend observed for iloperidone in the ST phase was also observed in the LT phase with 5 of the 6 SNPs in patients who switched from placebo or ziprasidone to iloperidone at the beginning of the open-label phase

Figure 3. Study Design

Discovery of the association of iloperidone efficacy with 6 SNPs.
Analysis of the 6 SNPs in patients treated with iloperidone only during the extension phase.
N shows the number of patients who entered and completed the extension phase.

Methods

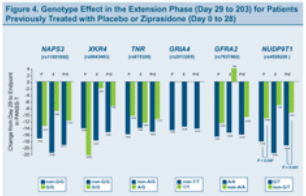
- The design, conduct, and overall results of the clinical study have been reported previously.[5] Briefly, schizophrenia patients were randomly assigned to iloperidone 12 mg twice a day, ziprasidone 80 mg twice a day, or placebo. At day 29, those patients choosing to enter the long-term phase of the trial began iloperidone treatment (12 mg once or twice daily)
- Response to treatment was measured by change in the Positive and Negative Syndrome Scale Total (PANSS-T) score
- Analysis of the genotype effect was performed using a general linear model with baseline value as a covariate
- For patients who switched to iloperidone, PANSS-T was analyzed at the end of the study (day 203) as improvement from the baseline of the extension phase (day 29)

Results

Individual SNPs

- For 5 of the 6 SNPs, the same genotype trend observed for iloperidone-treated patients in the short-term phase was also observed in the long-term phase for patients who switched from placebo or ziprasidone to iloperidone at the beginning of the open-label phase (Figure 4)
- The effect of one SNP (rs2513265, *GRIA4*) could not be assessed because the minor allele was not observed in any of the patients who completed the long-term phase after receiving either placebo or ziprasidone in the short-term phase (Figure 4)
- Statistical significance was reached for SNP rs4526226 (Figure 4), which had previously showed the stronger association with iloperidone efficacy in the short-term study (Figure 1)

Figure 4. Genotype Effect in the Extension Phase (Day 29 to 203) for Patients Previously Treated with Placebo or Ziprasidone (Day 0 to 28)

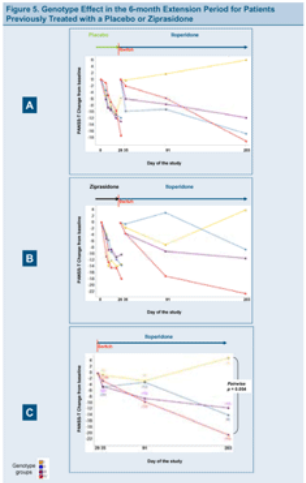


P= Placebo group, Z = Ziprasidone group.

Genotype groups

- Overall, patients from groups II, III, and IV but not from group I tend to improve after switching to iloperidone (Figure 5)
- As seen in the 28 day-phase treatment with iloperidone (Figure 2), patients from group IV who switched to iloperidone show the strongest response (Figure 5C)
- The same trend was observed regardless of the treatment [placebo (Figure 5A), or ziprasidone (Figure 5B)] that those patients had received during the short-term phase
- When combining data from patients from both the placebo and ziprasidone groups, a pairwise comparison of the genotypes associated with the highest (group IV) or lowest (group I) response provided a significance level of 0.054

Figure 5. Genotype Effect in the 6-month Extension Period for Patients Previously Treated with a Placebo or Ziprasidone



* These patients were treated in the short-term phase of the study with either a placebo or ziprasidone.

Discussion

- We studied 6 genetic markers associated with iloperidone efficacy, previously discovered in an analysis of the 28-day short-term phase of a phase III clinical trial[5]
- A new analysis was conducted in patients who had previously received either a placebo or ziprasidone during the 28-day short-term phase, and who were then treated with iloperidone in a 6-month extension phase
- These patients constitute an independent sample population since they were not part of the iloperidone-treated patients analyzed previously
- The analysis of each individual SNP showed the same genotype trend previously observed for iloperidone-treated patients, for 5 of the 6 genetic markers
- Statistical significance was reached for SNP rs4528226, which had previously showed the stronger association with iloperidone efficacy in the short-term study[5]
- We have defined 4 groups of genotype combinations (groups I to IV) based on the number of predictive genotypes associated with enhanced response, and showed that the probability of response to iloperidone treatment increased with the number of favorable genotypes carried by a patient[6]
- Despite the small number of patients who were studied in the open-label 6-month extension, the effect observed between the various genotype groups was consistent with the previous findings obtained with a different group of patients. For patients treated with iloperidone in the 6-month extension phase, a similar effect was observed regardless of the treatment (placebo, or ziprasidone) that these patients had received during the short term phase

Conclusion

- This study is a first step in validating the 6 iloperidone efficacy markers in an independent population
- The findings reported here support the application of pharmacogenomics to differentiate medication options and improve individualized treatments for patients affected with schizophrenia
- Additional pharmacogenomic analyses should be conducted in a large sample population to confirm and refine the predictive value and the clinical application of the 6 genetic markers associated with iloperidone efficacy, either individually or as a group

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Presented at the 162nd Annual Meeting of the American Psychiatric Association
May 16-21, 2009, San Francisco, CA

News Release

Vanda Pharmaceuticals to Present Data on Fanapt™ and tasimelteon at the 162nd American Psychiatric Association Annual Meeting

ROCKVILLE, MD., May 14/PRNewswire-FirstCall/ — Vanda Pharmaceuticals Inc. (Nasdaq: VNDA) announced today that it will present posters on its newly approved atypical antipsychotic, Fanapt™ (iloperidone), at the 162nd American Psychiatric Association (APA) annual meeting in San Francisco, California. Fanapt™ is indicated for the acute treatment of schizophrenia in adults. Vanda will also present two posters on tasimelteon at APA. Tasimelteon is an investigational compound in development for the treatment of circadian rhythm sleep disorders, including transient insomnia caused by jet lag.

The following two posters discussing data from Fanapt™ clinical trials will be presented at scientific poster sessions on Monday, May 18 from 9:00 am to 10:30 am.

NR1-033 *Efficacy of Iloperidone is Comparable to Risperidone in Analyses of a Placebo- and Risperidone-Controlled Clinical Trial for Schizophrenia.*

NR1-026 *The Comparative Efficacy of Iloperidone and Haloperidol Across Four Short-Term Controlled Trials.*

The following four posters discussing genetic and genomic studies in schizophrenia will be presented at scientific poster sessions on Monday, May 18 from 9:00 am to 10:30 am (NR1-095, NR1-058, NR1-092) and on Wednesday, May 20 from 3:00 pm to 5:00 pm (NR7-009).

NR1-095 *Effect of 6 genetic markers associated with iloperidone efficacy on long term clinical outcome of patients who switch to iloperidone.*

NR1-058 *Effect of polymorphisms in the dopamine receptor 2 gene on iloperidone efficacy for the treatment of patients with schizophrenia.*

NR7-009 *Common effect of antipsychotics on biosynthesis and regulation of fatty acids and cholesterol supports a role of lipid homeostasis in schizophrenia.*

NR1-092 *Selective estrogen receptor modulators share the antipsychotic gene expression profile, suggesting their potential in the treatment of schizophrenia.*

The following two posters discussing data from tasimelteon studies will be presented at scientific poster sessions on Wednesday, May 20 from 3:00 pm to 5:00 pm.

NR7-098 *Effect of a Period 3 (PER3) Polymorphism on Sleep Architecture in Phase Advanced Transient Insomnia.*

NR7-100 *Effect of Melatonin Agonist Tasimelteon on Sleep Parameters and Architecture in a Phase Advance Model of Transient Insomnia.*

About Vanda

Vanda Pharmaceuticals Inc. is a biopharmaceutical company focused on the development and commercialization of clinical-stage products for central nervous system disorders. For more on Vanda, please visit http://www.vandapharma.com.

About Fanapt™

Fanapt™ is an atypical antipsychotic agent indicated for the acute treatment of schizophrenia in adults. In choosing among treatments, prescribers should consider the ability of Fanapt™ to prolong the QT interval and the use of other drugs first. Prescribers should also consider the need to titrate Fanapt™ slowly to avoid orthostatic hypotension, which may lead to delayed effectiveness compared to some other drugs that do not require similar titration.

IMPORTANT WARNINGS and PRECAUTIONS: increased mortality in elderly patients with dementia-related psychosis; QT prolongation; neuroleptic malignant syndrome; tardive dyskinesia; hyperglycemia and diabetes mellitus; weight gain; seizures; orthostatic hypotension and syncope; leukopenia, neutropenia and agranulocytosis; hyperprolactinemia; body temperature regulation; dysphagia; suicide; priapism; potential for cognitive and motor impairment.

COMMONLY OBSERVED ADVERSE REACTIONS of FANAPT™ (>=5% and 2x placebo): dizziness, dry mouth, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia, and weight increased.

For more information on Fanapt™, please visit the detail station with the full US Prescribing Information, including Boxed Warnings and Important Safety Information, or visit our Web site at www.fanapt.com.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

Various statements in this release are “forward-looking statements” under the securities laws. Words such as, but not limited to, “believe,” “expect,” “anticipate,” “estimate,” “intend,” “plan,” “targets,” “likely,” “will,” “would,” and “could,” and similar expressions or words, identify forward-looking statements. Forward-looking statements are based upon current expectations that involve risks, changes in circumstances, assumptions and uncertainties. Vanda Pharmaceuticals Inc. is at an early stage of development and may not ever have any products that generate significant revenue. Important factors that could cause actual results to differ materially from those reflected in the company’s forward-looking statements include, among others: delays in the completion of Vanda’s clinical trials; a failure of Vanda’s products to be demonstrably safe and effective; Vanda’s failure to obtain regulatory approval for its products or to comply with ongoing regulatory requirements for its products; a lack of acceptance of Vanda’s products in the marketplace, or a failure to become or remain profitable; Vanda’s expectations regarding trends with respect to its costs and expenses; Vanda’s inability to obtain the capital necessary to fund its commercial and research and development activities; Vanda’s failure to identify or obtain rights to new products; Vanda’s failure to develop or obtain sales, marketing and distribution resources and expertise or to otherwise manage its growth; a loss of any of Vanda’s key scientists or management personnel; losses incurred from product liability claims made against Vanda; a loss of rights to develop and commercialize Vanda’s products under its license and sublicense agreements and other factors that are described in the “Risk Factors” section (Part II, Item 1A) of Vanda’s quarterly report on Form 10-Q for the fiscal quarter ended March 31, 2009 (File No. 001-34186). In addition to the risks described above and in Part II, Item 1A of Vanda’s quarterly report on Form 10-Q, other unknown or unpredictable factors also could affect Vanda’s results. There can be no assurance that the actual results or developments anticipated by Vanda will be realized or, even if substantially realized, that they will have the expected consequences to, or effects on, Vanda. Therefore, no assurance can be given that the outcomes stated in such forward-looking statements and estimates will be achieved.

All written and verbal forward-looking statements attributable to Vanda or any person acting on its behalf are expressly qualified in their entirety by the cautionary statements contained or referred to herein. Vanda cautions investors not to rely too heavily on the forward-looking statements Vanda makes or that are made on its behalf. The information in this release is provided only as of the date of this release, and Vanda undertakes no obligation, and specifically declines any obligation, to update or revise publicly any forward-looking statements, whether as a result of new information, future events or otherwise.

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