PD-299,685
A Novel Treatment for Hot Flashes

- Treatment of Vasomotor Symptoms Associated with Menopause
- Current Standard of Care is Hormone Replacement Therapy (HRT)
- Non-hormonal Mode of Action Offers an Alternative to Women Concerned About HRT

Valid as of November 30, 2006
**PD-299,685**

*Reduces the Number of Hot Flashes*

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### Adjusted Mean Change from Baseline Adjusted Mean Change from Baseline

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<th>Number of Hot Flashes</th>
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</tbody>
</table>

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**Placebo**

**PD 299685 5mg**

**PD 299685 15mg**

**PD 299685 30mg**

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Valid as of November 30, 2006
Alzheimer’s Points of Intervention

- Aβ Antibodies and RAGE
  Increase Clearance of Aβ

- Secretase Inhibitors
  Block Production of Aβ

- Tau Kinase Inhibitors
  Block Tangle Formation

- Cholesterol Modulation
  Lower Aβ Production

- Neuroprotection
  Increase Neuron Survival

- Neurorestoration
  Increase Neuron Function

Valid as of November 30, 2006
Compelling Approach: Potential Best-In-Class Therapy for Alzheimer’s Disease

Robust Portfolio of Other Opportunities

- RN624 – Acute and Chronic Pain (Entering Phase 2)
- Antibodies Related to the Prevention of Chemo-induced Cachexia
- Rich Discovery Pipeline

Valid as of November 30, 2006
**RN1219**

Reduces Plaque, Improves Cognitive Function

- **AD Control**
- **1 Month**
- **2 Months**
- **3 Months**

*Results presented using glycosylated Murine anti-Aβ antibodies - same target as RN1219*


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Valid as of November 30, 2006
Second Strategic Collaboration in Alzheimer’s Disease

Highly Complementary to Rinat and In-House Approaches

Novel Mechanism Targeted: Receptor for Advanced Glycation End-products (RAGE)

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RAGE Therapies

TTP4000 or TTP488

AD Brain Plaques
Activated Inflammatory Cells
Beta-Amyloid

Valid as of November 30, 2006
**TTP488 Results**

**Prevention Model**
Begin Treatment at 6 Months Before Plaque Deposition is Initiated

**Therapeutic Model**
Begin Treatment at 12 Months after Plaque Deposition Has Initiated

Valid as of November 30, 2006
Schizophrenia
Points of Intervention

PDE-10 Inhibitors
Directly Activate the Striatum to Increase Cortical Feedback

D₂ Antagonists
Increase Striatal Activity by Blocking Dopamine (DA) Inhibition

Several Early-Stage Mechanisms

5-HT₂C Agonists
Increase Striatal Activity by Inhibiting Dopamine Cell Firing

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PDE-10 Rationale

- Gene Family Initiative
- PDE-10 Identified and Cloned Localized to Brain
- High-Throughput Screen Identified Inhibitors
- Crystal Structure Obtained

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PDE-10 Inhibitors
Active in Schizophrenia Models

Avoidances

MP - 10 (mg/kg, SC)

Valid as of November 30, 2006
Groundbreaking Collaborations

- Stephen V. Faraone, SUNY, “International Multi-Center ADHD Genetics Project.”
- Pablo V. Gejman, Northwestern, “Genome-Wide Association Study of Schizophrenia.”
- John Rice Kelsoe, UCSD, “Whole Genome Association Study of Bipolar Disorder.”
- Patrick Francis Sullivan, UNC, “Major Depression: Stage 1 Genome-wide Association in Population-Based Samples.”
Neuroscience Vision

We will Change Society by Lifting the Burden of Neuropsychiatric Disease

Valid as of November 30, 2006