C-10068: Novel Morphinan with a Unique Pharmacological Profile

Philip Graham, PhD., Ara Aslanian PhD, Sophia Nguyen, Vinita Uttamsingh PhD, Adam Morgan PhD, Gary Bridson, LuAnn Sabounjian, James Shipley MD
Concert Pharmaceuticals
C-10068: Novel Anti-Epileptic Therapy

- Based on dextroETHorphan identified at NIH in 1990s (Tortella)
  - Evidence of anticonvulsant properties
  - Low oral bioavailability
  - No human experience

- C-10068 incorporates deuterium
  - Intrinsic pharmacology unchanged
  - 3X increase in oral bioavailability (rat)
  - Metabolite formation greatly reduced

- Unique pharmacological profile
  - Acts at multiple targets
  - Efficacy data in various preclinical models of seizure, pain and depression

- Research collaborations with NINDS and WRAIR

- Pre-IND development on-going

---

NINDS: National Institute of Neurological Disorders and Stroke
WRAIR: Walter Reed Army Institute of Research
C-10068: Efficacy in Models Conducted at NINDS

- Maximal Electroshock Model
  \( ED_{50} \approx 20 \text{ mg/kg ip} \) in mice and rats
  - Compared to dextromethorphan greater potency, longer duration of action and wider therapeutic index
- 6Hz Model
  - Partial protection
- Formalin pain model in mice
  - 75% reduction in chronic/inflammatory phase at 22 mg/kg (MES \( ED_{50} \))
- Neuroprotection Assay \textit{(in vitro)}
  - Protects against NMDA and kainic acid induced neurotoxicity

Data generated by NINDS anti-convulsant screening program; Presented at Epilepsy Pipeline Meeting 2011
C-10068 Binds to Pharmacologically Important Targets

- Single-point (10µM) binding screen of 68 targets (Ricerca Lead Profiling screen)
- Significant binding detected for potential target sites expressed in CNS

Binding at 10µM (% Inhibition)

![Graph showing binding at 10µM](image)

Binding to α1a, α2a, α2d adrenergic receptors detected, not shown.

>50% inhibition considered significant in this assay
C-10068 Exhibits More Potent Binding to Human Sigma Receptor than DM

Human Jurkat cells, ligand: 8 nM [³H] pentazocine

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC$_{50}$, nM</th>
<th>K$_i$, nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-10068</td>
<td>190</td>
<td>150</td>
</tr>
<tr>
<td>DM</td>
<td>1100</td>
<td>920</td>
</tr>
</tbody>
</table>

~6X
C-10068 Inhibits Serotonin Transport in Human Platelets

- C-10068 & dextroETHorphan inhibit serotonin transport more potently than dextrorphan (DX)

- Recent studies\(^1\) suggest serotonergic agents may reduce risk of sudden death following seizure

### Table

<table>
<thead>
<tr>
<th>Compound</th>
<th>(\text{IC}_{50}, \text{nM})</th>
</tr>
</thead>
<tbody>
<tr>
<td>dextroETHorphan</td>
<td>201</td>
</tr>
<tr>
<td>C-10068</td>
<td>146</td>
</tr>
<tr>
<td>DX</td>
<td>2589</td>
</tr>
</tbody>
</table>

\(^1\) Faingold C. Epilepsy & Behavior 22 (2011) 186–190
DX More Potent Inhibitor of rhNMDA Receptor Functional Activity than DM or C-10068

Cloned human NMDA receptors stably expressed in HEK293 cells analyzed by FLIPR

DX is the only compound that had measurable IC$_{50}$ in this assay
Human Liver Microsome Assay Demonstrates Dramatically Reduced Formation of Dextrorphan From C-10068 Versus DM

- Contribution from structural change and incorporation of deuterium
- Rate of formation \( (V_{\text{max}}) \) of DX from C-10068 ~ 1/6\(^{\text{th}}\) the rate at which DX is produced from DM
- Efficiency \( (V_{\text{max}}/K_m) \) of formation of DX from C-10068 ~ 1/2 compared to DM

<table>
<thead>
<tr>
<th>Compd ID</th>
<th>( K_m ) µM</th>
<th>( V_{\text{max}} ) ng/min/mg</th>
<th>( V_{\text{max}}/K_m ) mL/min/mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextromethorphan</td>
<td>9.5</td>
<td>19.4</td>
<td>7.5</td>
</tr>
<tr>
<td>DextroETHorphan</td>
<td>6.3</td>
<td>7.6</td>
<td>4.2</td>
</tr>
<tr>
<td>C-10068</td>
<td>3.0</td>
<td>3.1</td>
<td>3.5</td>
</tr>
</tbody>
</table>
- Non-convulsive seizures (NCS) associated with poor prognosis following traumatic brain injury
- Rat Model of Penetrating Ballistic-like Brain Injury (PBBI)
  - 30 minutes after injury groups of 16 rats treated with C-10068 at 1, 2.5 or 5 mg/kg/h iv infusion or saline for 72 hours.
  - Continuous EEG monitoring - NCS start around 16 hours in about ¾ of animals
C-10068 Infusion Dose-dependently Decrease NCS

- Additional studies in progress at WRAIR
  - Histopathology from completed PBBI study
  - In vivo neuroprotection tests (catwalk, rotarod and Morris water maze) at various timepoints following injury
C-10068 Antidepressant Effect is Comparable to Imipramine Positive Control in Forced Swim Test Model

- Drug administered ip 30 minutes before test
- Time to first bout of latency for C-10068 also comparable to positive control
- Potentially important attribute given co-morbidity of epilepsy and depression

C-10068: Summary

- Novel morphinan stabilized by incorporation of deuterium
  - Oral bioavailability increased by three-fold in rat
  - Reduced formation of undesired metabolite (dextrorphan)

- Efficacious in various animal models
  - Maximal electroshock, 6Hz
  - Non-convulsive seizures following TBI
  - Inflammatory and neuropathic pain
  - Depression

- Distinguishing characteristics
  - Unique pharmacological profile
    - Acts at multiple CNS targets
  - Protection against NMDA and kainic acid neurotoxicity (*in vitro*)
  - Potential antidepressant effect
  - Serotonergic properties may be protective against sudden death
Acknowledgments

- **NINDS – Anticonvulsant Screening Program**
  - James Stables PhD
  - Tracey Chen PhD
  - Jeff Jiang PhD
  - H. Steve White PhD

- **WRAIR**
  - Frank Tortella PhD
  - May Lu, PhD
  - Deborah Shear, PhD
  - Major Kara Schmid

- **Chemistry**
  - Adam Morgan, PhD
  - Craig Masse, PhD

- **Bioanalytical**
  - Changfu Cheng, PhD
  - Gary Bridson

- **DMPK**
  - Vinita Uttamsingh, PhD
  - Richard Gallegos
  - Sophia Nguyen
  - Medicilon

- **Pharmacology**
  - Ara Aslanian, PhD

Philip Graham, Ph.D.
pgraham@concertpharma.com
Tel. 781-674-5246