KINDOLOR

A new molecular entity for treating chronic pain and cancer
Commercial Opportunity for Neuropathic Pain

Market value and future leaders in the clinical management of chronic pain

- The chronic pain market, comprised of both nociceptive and neuropathic pain treatments, was worth $24 billion in 2007**
- In 2008, the diabetic neuropathic pain (DNP) market on its own was valued at $2.9 billion and is forecasted to grow to $6.3 billion by 2016**
- Lyrica (pregabalin), Neurontin (gabapentin) and Cymbalta (duloxetine) are the current market leader for treatments for chronic pain. 30% effective at best.
  - 2010 sales for Lyrica were $821 million, and for Cymbalta for all indications, 2010 sales were almost $4 billion.
- Patent protection for both Cymbalta and Lyrica terminate in the near future (Cymbalta, June, 2013 and Lyrica between October, 2013 and December, 2018

Forecasted Pain Market Share (by value) in 2016**

** Datagroup, “Commercial Insight: Pain Market Overview” October 2010
Great Unmet Medical Need

The next generation of pain therapies must improve on **efficacy** and **safety**

- Huge commercial value but treatment is challenging due to heterogeneous patient population
- Need for compounds with improved efficacy
  - Large untreated patient population
  - *It is estimated that only 10% of diabetic neuropathic pain patients are successfully treated ***
- Improved tolerability / side effect profile needed
  - Current agents are deficient because:
    - Abuse liability
    - CNS side effects (e.g., sedation; psychiatric disturbances)
    - Cardiovascular side effects
    - GI disturbances
    - Renal and hepatic toxicity
- Better clinical translation and identification of responders needed
  - Lohocla has a research program focused on identifying possible biomarkers for pain

** Pipeline and Commercial Insight: Neuropathic Pain. Datamonitor, 2008 **
Etiology of Chronic Pain Syndromes

Chronic pain syndromes are a debilitating result of multiple maladaptations in the body to deal with responses to injury of nerves, spinal cord or brain.
**Program Summary**

**Chronic Pain**
Chronic pain is defined as a debilitating sensory and emotional state associated with tissue damage, and persisting longer than the temporal course of natural healing. Chronic pain syndromes such as diabetic neuropathy, fibromyalgia, referred pain syndromes resulting from mechanical nerve injury or tumors, inflammation related nerve damage, cancer treatment related pain syndromes and many others can be aggregated etiologically as arising from a maladaptive attempt of the peripheral and central nervous systems to deal with damage to the sensory nerves.

**Pharmacology of Kindolor Approach to the Treatment and prevention of Chronic and/or neuropathic pain**
Lohocla designed a single molecule which would simultaneously reduce the over-activity of NMDA (NR1-NR2B) receptors and the Nav 1.7 and Nav 1.8 sodium channels which conduct information along sensory and other nerves and act as an agonist at delta opiate receptors in chronic pain syndromes.

A screen of over 60 other receptors/channels demonstrated that most of these showed no significant binding of Kindolor at concentrations below 10 μM.

**In-vivo Efficacy**
- Reverses hyperalgesia in rat diabetic neuropathy model (STZ)
- Reverses hyperalgesia in rat nerve injury model (SNL)
- Reverses hyperalgesia in mouse inflammatory pain model (Formalin Test)
- Reverses hyperalgesia in rat inflammatory pain model (CFA)
- Reverses hyperalgesia in cancer chemotherapy-induced pain (cisplatin)
- Reverses hyperalgesia in another cancer chemotherapy-induced pain model (paclitaxel)
- Prevents the development of cancer chemotherapy-induced pain (cisplatin)
- Prevents the development of inflammation induced chronic pain (CFA)
- Potentiates effects of other analgesics (e.g., morphine and aspirin)
- No effect on normal acute pain perception (i.e., not an antinoceptive drug)
- No evidence of tolerance following chronic administration
- No evidence of dependence liability
Program Summary (Cont’d)

Absorption: Kindolor, after oral administration, is absorbed in the intestine through active transport via the PEPT1 transport system. At the proposed therapeutic dose.

Distribution: A formal 14C mass-balance study is planned and generally required for registration but not necessary for opening of our IND. Studies have shown that negligible concentrations of Kindolor were evident in brain after oral or intraperitoneal injection. Therefore, it is predicted that minimal CNS side effects would be expected.

Metabolism: Kindolor is metabolized by hydroxylation and glucuronidation and these biotransformed products are excreted in the urine and feces. It is estimated that 90% or more of Kindolor which enters the circulation is metabolized prior to excretion.

Bioavailability: Kindolor has good oral bioavailability and during its transit in the circulatory system is mostly protein bound. In monkeys, the half-life of Kindolor is 7-8 hours and 1.5 hours in the rat. In the rat, bioavailability studies demonstrated that therapeutic blood levels of Kindolor in the micro molar range were achieved after either oral or intraperitoneal administration given at 20-50 mg/kg.

Animal Safety Assessment

-Non-GLP Maximum tolerated dose (MTD), followed by seven day repeated dose toxicity and toxico-kinetic analysis is complete. A GLP 28 day repeat dose toxicity and toxico-kinetic analysis with 14 day recovery is also complete. Little or no toxicity has been noted in rats or mice administered Kindolor. Final reports have been issued.

-These toxicology studies showed that Kindolor’s “No Observed Adverse Effects (NOAEL)” on repeated administration to rats is at or above 2,000 mg/kg/day. These and other data, led us to estimate the therapeutic index for Kindolor to be greater than 50 which is considered very favorable in the eyes of the FDA.

-No activity of Kindolor was noted at concentrations of 50µM or less on the hERG channel, which is a potassium channel important in heart function.

-The bacterial mutation test (Ames Test) indicated no teratogenic potential for Kindolor.

-
**Kindolor Patent Status:**
**Composition, Synthesis and Use**

**Compounds, Compositions & Method Patent**

US 6,962,930
Date of Patent: November, 2005
Patents corresponding to U.S. Patent No. 6,962,930 are in force in France, Germany, Switzerland and the United Kingdom.

**Methods for Treating Chronic Pain.**

U.S. 7,923,458
Date of Patent: April, 2011


**Methods for Treating Peripheral Neuropathic Pain**

*Pending application U.S. Publication No. 2011/0184018A1*

Drafts of two other applications to expand the range of compounds and potential therapeutic targets beyond the subject matter of the issued patents and pending application. The new applications, designated TBK-105 and TBK-106 are intended to cover a much broader range of compounds for the treatment of pain and cancer metastasis than simply Kindolor and its esters. The TBK-105 case also is intended to cover uses for treatment of tumor metastasis, in addition to Chemotherapy-induced neuropathy. The TBK-106 case relates to certain Kindolor analogs (replacing one or both of the phenyl groups on the urea moiety with an alkyl group) that have been identified as selective δ and κ opioid receptor ligands.
Kindolor: Molecular Design and

*In Vitro* Proof of Action
Multimodal Treatment of Chronic Pain Disorders with Kindolor

**Opioid Receptor System**
- Delta receptors (DOR) are expressed in primary sensory neurons.
- Kindolor activates DOR and produces analgesia.

**Other**
- Acid Sensing Ion Channels
- Purinergics
- Monoamines
  - All contribute to development of chronic pain

**Glutamate**
- Glutamate receptors play a crucial role in modulating pain pathways.
- Chronic pain is maintained by a state of sensitization within the CNS that is mediated in part by glutamate binding to NMDA receptors.
- Kindolor antagonizes NMDA receptors and relieves pain in rodent models.

**Transient Receptor Potential (TRP) Channels**
- TRPV1 is upregulated in a number of painful inflammatory disorders.
- TRPV1 channels transduce noxious temperature and chemical stimuli.
- TRPV1 KO are less susceptible to certain pain modalities.
- Activation of TRPA1 channels causes pain, while TRPA1 deficient mice have impaired nociceptive responses.

**Endocannabinoid System**
- The endogenous cannabinoid system overlaps with pain circuitry and suppresses pain.
- Effects of cannabinoid system on pain are mediated by both the central and peripheral nervous systems.
- CB2 receptor agonism reverses inflammatory and neuropathic pain.
- Blocking CB1 receptors produces hyperalgesia.
- Preliminary evidence shows that a derivative of Kindolor activates this system.

**Kindolor blocks Voltage Gated Na\textsubscript{v} Channels**
- Na\textsubscript{v}1.7 is upregulated in neuropathic and chronic inflammatory models.
- Post-injury hyperexcitability to DRG neurons results, in part, from increased expression of Na\textsubscript{v}1.7.
- Na\textsubscript{v}1.7 KO mice do not develop hyperalgesia to a variety of insults.
- Thermal and visceral pain responses induced by inflammatory mediators are impaired in Na\textsubscript{v}1.8 channel KOs.
- Na\textsubscript{v}1.8 channels are nearly exclusively localized to C-fibers and DRG neurons.
## Affinities of Kindolor Acting as an Antagonist at NMDA Receptor Subtypes

<table>
<thead>
<tr>
<th>NMDA Subunit Heteromers</th>
<th>IC$_{50}$ (µM)</th>
<th>$K_i$ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR1a/NR2A</td>
<td>12.3</td>
<td>4.9</td>
</tr>
<tr>
<td>NR1a/NR2B</td>
<td>18.8</td>
<td>0.5</td>
</tr>
<tr>
<td>NR1a/NR2C</td>
<td>31.5</td>
<td>--</td>
</tr>
<tr>
<td>NR1a/NR2D</td>
<td>45.1</td>
<td>--</td>
</tr>
<tr>
<td>NR1a/NR3a</td>
<td>6.3</td>
<td>--</td>
</tr>
</tbody>
</table>

NMDA subunit heteromers were expressed in HEK293 cells. NMDA-induced currents were elicited in the presence of saturating concentrations of agonist (glutamate or NMDA) and glycine. IC$_{50}$ values were calculated from Kindolor concentration-response curves using non-linear curve fitting. $K_i$ values were calculated using the Cheng-Prusoff equation.
Affinities of Kindolor for the Inactivated State of Voltage-gated Sodium Channels (VGSC)

<table>
<thead>
<tr>
<th>Channel</th>
<th>IC$_{50}$ (µM)</th>
<th>$K_i$ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na$_V$1.2</td>
<td>--</td>
<td>15.6$^a$</td>
</tr>
<tr>
<td>Na$_V$1.7</td>
<td>--</td>
<td>9.6$^a$</td>
</tr>
<tr>
<td>Na$_V$1.5</td>
<td>&gt;50$^b$</td>
<td></td>
</tr>
<tr>
<td>Na$_V$1.8</td>
<td>~0.8$^c$</td>
<td></td>
</tr>
<tr>
<td>hERG</td>
<td>--</td>
<td>&gt;50</td>
</tr>
</tbody>
</table>

VSCG depolarizing currents were measured in $^a$CHO cells expressing Na$_V$1.2 or Na$_V$1.7 α-subunits, Nav 1.7 demonstrates use dependent inhibition at Kindolor concentrations as low as 1 micromolar. $^b$CHO-Na$_V$1.5 stable cell line or $^c$isolated rat dorsal root ganglia.
## Selectivity of Kindolor for the Delta Opiate Receptor

### Affinities of Kindolor for Opiate Receptor Subtypes

<table>
<thead>
<tr>
<th>Receptor Subtypes</th>
<th>K(binding)</th>
<th>IC$_{50}$ (function)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$ Receptor</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>$\delta$ Receptor</td>
<td>4.5 $\mu$M</td>
<td>3.3 $\mu$M</td>
</tr>
<tr>
<td>$\kappa$ Receptor</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

N.S. indicates no measureable inhibition of binding or inhibition of functional activity with Kindolor at concentrations of 10 $\mu$M.
Kindolor is Selective and Does Not Effect Related and "Nuisance" Receptors

<table>
<thead>
<tr>
<th>Function</th>
<th>Na\textsubscript{v}1.8</th>
<th>Na\textsubscript{v}1.7</th>
<th>NR1-NR2B NMDA receptor glycine site</th>
<th>(\delta)-opioid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>800 nM</td>
<td>9.0 (\mu)M*</td>
<td>500 nM</td>
<td>3.3 (\mu)M</td>
</tr>
<tr>
<td>(K_i)</td>
<td>(K_i)</td>
<td>(K_i)</td>
<td>(EC_{50})</td>
<td></td>
</tr>
</tbody>
</table>

* Inactivated state – inhibition increases with rapid discharge

Indicates no significant effect at concentrations <10 \(\mu\)M (1° binding) or higher (2° functional screening)

| D1 | D2 | D3 | D4 | D5 | M1 | M2 | M3 | M4 | M5 | H1 | H2 | H3 | H4 | 5-HT\textsubscript{1A} | 5-HT\textsubscript{1B} | 5-HT\textsubscript{1D} | 5-HT\textsubscript{1E} | 5-HT\textsubscript{2A} | 5-HT\textsubscript{2B} | 5-HT\textsubscript{2C} | 5-HT\textsubscript{3} | 5-HT\textsubscript{6A} | 5-HT\textsubscript{6} | 5-HT\textsubscript{7} | \(\alpha\)1A | \(\alpha\)1B | \(\alpha\)1D | \(\alpha\)2A | \(\alpha\)2B | \(\beta\)1 | \(\beta\)2 | \(\sigma\)1 | \(\sigma\)2 | Ca\textsuperscript{2+} Channel | V1A | DAT | NET | SERT | GABA\textsubscript{A} | mGluR5 | EP2 | A2B2 | A2B4 | A3B2 | A3B4 | A4B2 | A4B4 | \(\mu\)-opioid | NMDA (PCP site) | NMDA (glutamate) | CB1 | CB2 | Na\textsubscript{v}1.2 | Na\textsubscript{v}1.5 | hERG |
Kindolor

In-Vivo Studies of Efficacy
A Single Dose of Kindolor Reverses Chronic Pain in the Complete Freund’s Adjuvant Induced Inflammatory Pain Model

Nonlinear Regression analysis indicates, ED$_{50}$=22.0 ± 6.5 mg/kg. Adjusted R$^2$=0.298. N=16, 6,13,10, 11 for 0, 17.5, 32.5, 50, 75 mg/kg Kindolor group. *, significant difference compare to vehicle (zero Kindolor) group.
A Single Dose of Kindolor Reverses Chronic Pain in the STZ Induced Diabetic Neuropathy Pain Model

**Dose response effect**

Regression analysis determined that the ED$_{50}$ of Kindolor is $22.0 \pm 5.0$ mg/kg orally. Adjusted $R^2 = 0.9415$. N=14, 7, 8, 6, 7, 6 for 0, 17.5, 35, 32.5, 40, 75 mg/kg Kindolor group.

**Time course of effect**

#, p < 0.01 by one way ANOVA post hoc test, †, p<0.1. N=19, 9, 7, 8, 8, 7 for control, vehicle, 0.5h, 1.5h, 2.5h, 4.0h group.
Kindolor Efficacy in Neuropathic Pain / Nerve Injury Model

Kindolor reverses mechanical pain in the Spinal Nerve Ligation neuropathic pain model.

In male SD rats, the right L5 and L6 spinal nerves are tightly ligated. Two weeks after SNL surgery the mechanical pain threshold is measured by von Frey test. When Kindolor is not present (0 h), rats experience severe mechanical pain in this model. Kindolor (75 mg/kg, ip) completely reverses mechanical pain (allodynia), an effect that lasts up to 4 hrs.

* p<0.05 vs. 0 h group
Kindolor Efficacy in a Mouse Inflammatory Pain Model

Formalin (0.5%) is injected into the hind foot (intraplantar) of male CF1 mice.

Measurements of licking and chewing of injected paw are made during 30 min time period 10 min after formalin injection (inflammatory phase).

A more prolonged period (about 20 to 30 min) of licking ensues which constitutes the chronic phase (inflammatory) and is caused by the release of inflammatory mediators from the damaged tissue and nerve endings.

Kindolor (75 mg/kg, ip) administered 60 min prior to measurements almost completely blocked hyperalgesia.

* p<0.05 vs. Kindolor treatment group
A Single Dose of Kindolor Reverses Chronic Pain in a Cisplatin (cancer chemotherapeutic) Induced Neuropathy Pain Model

Kindolor was given orally. One Way ANOVA followed by Fisher LSD test revealed an overall significant difference (P=0.035).
A Single Dose of Kindolor Reverses Chronic Pain in a Paclitaxel (cancer chemotherapeutic) induced neuropathy pain model

Two Way ANOVA followed by multiple comparison with Bonferroni t-test revealed, Kindolor treatment produced a significant effect compared to vehicle treatment, *p = 0.02.
Kindolor Potentiates the Effects of Analgesics

- Opiates
- Salicylates
Kindolor Potentiates the Effects of Morphine

Combining “ineffective” doses of Kindolor and morphine results in a significant analgesic response in the CFA rat inflammatory pain model.

Complete Freund's Adjuvant (CFA) (0.1 ml) is injected into the rat's right hind paw (intraplantar) to produce inflammation.

The inflammatory pain response is evident within 24 hours and lasts up to 4 days as measured by the von Frey test. The non-injected paw serves as the control.

Experiments are done 48 hours after CFA injection with Kindolor and morphine administered 60 and 30 min before the test, respectively.

Although neither Kindolor nor morphine given alone at these doses produced a significant analgesic response, the combination of these two drugs reversed the pain response back to normal levels.

* p<0.05 compared to vehicle / vehicle

# NS (not significant) compared to non-injected paw (complete reversal)
Kindolor Synergizes with the Effects of Aspirin

Combining “ineffective” doses of Kindolor and aspirin results in a significant analgesic response in a diabetic neuropathic pain model.

Streptozotocin (STZ) 50 mg/kg, ip
Given to produce diabetes

STZ is toxic to β cells in the pancreas that produce insulin

Rats are hyperglycemic (~600 mg/dl) within 2 days of STZ, an effect that lasts for > 2 weeks.

von Frey testing is conducted 2 wks post-STZ treatment.

Behavioral testing occurred 60 min after administration of vehicle, Kindolor, aspirin or the combination of Kindolor and aspirin.

*p<0.05 compared to control group (no STZ treatment)
# NS compared to vehicle treatment group
** NS compared to non-injected paw (complete reversal)
Kindolor Does Not Alter “Normal” Pain Perception

Kindolor does not prevent the perception of normal acute pain

The formalin test, which involves injection of 0.5% formalin into the mouse hind paw, elicits a distinct behavioral profile which is characterized by licking of the affected paw immediately following the formalin injection. Mice intensely lick the paw for approximately for the first 5 min of the test. This initial behavior is considered phase 1 (acute pain response) and is thought to be mediated primarily by direct chemical activation of local C-fibers.

Kindolor (75 mg/kg, ip) does not interfere with the perception of acute irritant-induced pain nor disrupt “normal” pain processing.

Kindolor is not a classic “analgesic” like morphine or an anesthetic, but is an effective antihyperalgesic.
## Efficacy of Kindolor vs. Standard of Care

Kindolor shows greater potency than Neurontin, Lamictal, Lyrica and Cymbalta when given orally within the diabetic neuropathy model

<table>
<thead>
<tr>
<th>Drug</th>
<th>Kindolor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Molecular Weight</strong></td>
<td></td>
</tr>
<tr>
<td>334</td>
<td>256</td>
</tr>
<tr>
<td><strong>ED$_{50}$ (mg/kg)</strong></td>
<td></td>
</tr>
<tr>
<td>10-20</td>
<td>45 or 30</td>
</tr>
<tr>
<td><strong>ED$_{50}$ (mmol/kg)</strong></td>
<td></td>
</tr>
<tr>
<td>0.03-0.06</td>
<td>0.17 or 0.12</td>
</tr>
<tr>
<td><strong>Treatment method</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Test method in diabetic neuropathy model</strong></td>
<td></td>
</tr>
<tr>
<td>Tail flick and hot plate tests after 4 weeks of STZ treatment</td>
<td>paw pressure test</td>
</tr>
</tbody>
</table>

*NOTE: Cymbalta and Lamictal were administered i.p. which produces higher plasma drug levels compared to oral (p.o.) treatment. Thus, the ED$_{50}$ values for these medications are exaggerated by comparison to the medications administered p.o.*
Summary of the Prevention of Chronic Pain Development by Kindolor in Rat Models
Kindolor Prevented the Development of Allodynia (Chronic Pain) Due to Inflammation

Note: Student t-test is used to compare the pain threshold between group, and paired t-test is used to compare the pain threshold within group. Kindolor does not affect pain threshold in uninflamed paw.
Repeated oral Kindolor prevented the development of neuropathic pain in cisplatin induced neuropathic pain model

Two way repeated measure ANOVA revealed, there is a statistically significant difference (P = 0.023) between the two different treatments, Kindolor and vehicle. The individual p values shown in the graph are for Kindolor versus vehicle and are calculated by the multiple comparison method. There are also significant differences detected in the pain threshold in the cisplatin and vehicle group (day 15, 19, 25, 32 vs. day 0, therefore cisplatin), but no significant differences in pain threshold between the cisplatin and Kindolor group compared to the Day 0 values (prior to cisplatin injection).
Kindolor: Summary of Preclinical Efficacy

- Kindolor was designed to interact with three systems responsible for the development of chronic pain
  - Selective and lacks significant affinity at 68 related or “nuisance” receptors including hERG and Nav1.5
- Kindolor binds to its molecular targets to produce oral efficacy in multiple preclinical models of chronic pain
  - Reverses hyperalgesia in rat diabetic neuropathy model (STZ)
  - Reverses hyperalgesia in rat nerve injury model (SNL)
  - Reverses hyperalgesia in mouse inflammatory pain model (Formalin Test)
  - Reverses hyperalgesia in rat inflammatory pain model (CFA)
  - Reverses hyperalgesia in cancer chemotherapy-induced pain (cisplatin)
  - Reverses hyperalgesia in another cancer chemotherapy-induced pain model (paclitaxel)
  - Prevents the development of cancer chemotherapy-induced pain (cisplatin)
  - Prevents the development of inflammation induced chronic pain (CFA)
  - Potentiates effects of other analgesics (e.g., morphine and aspirin)
  - No effect on normal acute pain perception (i.e., not an antinoceptive drug)
  - No evidence of tolerance following chronic administration
- Kindolor has improved tolerability profile vs. Standard of Care (SOC)
  - No evidence of dependence liability
  - No CNS-related side effects (e.g., sedation, disturbances in mood and cognition)
  - No noted or anticipated cardiovascular, GI, renal or hepatic complications
Kindolor

Absorption, Distribution, Metabolism and Elimination (ADME)
Rat Plasma Levels of Kindolor at Escalating Doses of Orally Administered Kindolor

Note: Data were generated from naive male Sprague-Dawley rats treated with various doses of Kindolor. Sample time is 60 minutes following treatment, except 32.5 and 100 mg/kg groups are sampled at 90 min. Non-linear regression analysis, Adjusted $R^2 = 0.8364$
In-Vitro Metabolism

- The major CYP450 enzymes responsible for hydroxylation of Kindolor \textit{in vitro} are 2C9 and the 2C9*2 variant.

- Kindolor is metabolized 90\% by glucuronide conjugation (microsomal and cytosolic) and 10\% via hydroxylation.

- Low affinity for CYP enzymes implies low likelihood of drug-drug interactions.
Kindolor Has a Favorable Cross Species / PK Profile

• Kindolor when administered orally has a 7-8 hr half-life in monkeys and 1.5 hr in rats

  • Oral administration of Kindolor at “therapeutic” doses of 50 mg/kg results in:

    – Rats: average peak plasma levels of 12 µM at 50 mg/kg (1 hr post-drug administration)

    – Monkeys: mean peak plasma levels of 38 µM at 50 mg/kg (1 hr post-drug administration)
Calculations of Plasma Levels of Kindolor, when Kindolor is Orally Administered at a Dose Equivalent to Its ED$_{50}$ for Reversing Chronic Pain

Dose-Response of Antihyperalgesic Effects of Kindolor in the STZ Model of Diabetic Neuropathy and Plasma Levels of Kindolor Measured 90 Minutes after Oral Administration of Kindolor at Escalating Doses
Kindolor Does not Readily Penetrate the CNS

Even high doses of Kindolor (1000 mg/kg, po) produce very low drug levels in brain

- Low likelihood of CNS-related side effects and complications
  - No sedation or disturbances in motor coordination
  - No psychiatric disturbances or cognitive impairment
  - No interactions with sedatives (e.g., ethanol)

Plasma Kindolor (ng/mL) 50 min after Kindolor administration:
- 15µM (vehicle)
- 7,033 ng/mL (Kindolor 50 mg/kg, po)
- 20,966 ng/mL (Kindolor 150 mg/kg, po)
- 57,600 ng/mL (Kindolor 1000 mg/kg, po)

Brain Kindolor (ng/g) 50 min after Kindolor administration:
- 49 ng/g (vehicle)
- 139 ng/g (Kindolor 50 mg/kg, po)
- 177 ng/g (Kindolor 150 mg/kg, po)
- 127μM (Kindolor 1000 mg/kg, po)
Safety Assessment of Kindolor in the Rat

• Non-GLP Maximum tolerated dose (MTD), followed by 7-day repeated dose toxicity and toxico-kinetic analysis is completed. A GLP 28-day repeat dose toxicity and toxico-kinetic analysis with 14-day recovery is also complete. Final reports have been issued.

• These studies showed that Kindolor’s “No Observed Adverse Effects (NOAEL)” on repeated administration to rats was at a dose of 2,000 mg/kg body weight/day. This and other data, led us to estimate the therapeutic index for Kindolor to be greater than 50.

• Toxico-kinetics were also assessed in the above GLP studies. In general, females had a higher Cmax on days 1 and 7.

• There was no effect on the Nav 1.5 channel which is a channel important for normal cardiac function.

• Mean Body Weight and Net Body Weight Gains: No significant variation was observed in any treatment groups in both phases.

• Food Intake (g/rat/day): No variations were observed in food intake measured in either phase at all the dose levels tested.

• Clinical Pathology Investigation (Phase II): No treatment-related variation in the hematological, clinical chemistry and urine parameters were observed in the rats treated with Kindolor in both sexes.

• Fasting Body Weights (phase II): No treatment-related variations were observed in the terminal fasting body weights at all the doses tested in phase II group rats.

• Gross Pathology: No gross lesions observed at necropsy in both the phases of the study.

• Conclusion: Results show, the "No Observed Adverse Effect Level (NOAEL)" for the Kindolor on repeated 7 days oral administration to Sprague Dawley Rats is 2000 mg/kg body weight/day under the testing conditions and doses employed.
Projected Dosing in Humans Comparable to SOC

• Extrapolated dosing in humans suggests that Kindolor would be administered by taking one tablet (325 mg) twice daily to control chronic pain
  - Based on normalization to body surface area in rats it is estimated that Kindolor will be administered 1-2 times per day in humans at ~ 325 mg/dose
  - Using body surface area and comparisons between pharmacokinetic data in rats versus monkeys, lower doses of Kindolor can likely be administered
  - This treatment paradigm is similar (and in some cases better) to the dosing schedules for Aspirin, Ibuprofen, Neurontin and Lyrica
  - We are also considering a slow or extended release capsule that would support a once daily dosing regimen in humans

<table>
<thead>
<tr>
<th>Medication</th>
<th>Recommended Human Dosage</th>
<th>Dosing Frequency</th>
<th>Daily Dosage (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>325 mg</td>
<td>4 x daily (QID)</td>
<td>975 mg</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>400 mg</td>
<td>4 x daily (QID)</td>
<td>1,600 mg</td>
</tr>
<tr>
<td>Lyrica</td>
<td>200 mg</td>
<td>3 x daily (TID)</td>
<td>600 mg</td>
</tr>
<tr>
<td>Neurontin</td>
<td>600 mg</td>
<td>3 x daily (TID)</td>
<td>1,800 mg</td>
</tr>
<tr>
<td>Kindolor</td>
<td>325 mg</td>
<td>2 x daily (BID)</td>
<td>650 mg</td>
</tr>
</tbody>
</table>
Kindolor: Other Clinical Indications

- Breast Cancer

- Bone cancer pain and osteoarthritis

- A small molecule derivative of Kindolor decreased alcohol preference in a chronic treatment paradigm

- Patents are being applied to protect structures related to Kindolor for their application to treat pain, drug addiction and relapse, neuroexcitatory disorders, depression and eating disorders
Cell Morphology of the Invasive and Non-Invasive Phenotype of the Mammary Tumor Cells (MCF10DCIS).

The invasive phenotype was generated during a 7 day culture in a 40% collagen/60% Matrigel transwell culture.
**Kindolor Reduces the Survival and Invasiveness of Human Breast Tumor Cells**

Panel A Demonstrates the lack of effect of 25 micromolar Kindolor on epithelial cells from a reduction mammoplasty (MCF12A).

Panel B Mammary Tumor Cells (MCF10DCIS) were used in a Collagen/Matrigel transwell invasiveness assay. On day 7 organoids were fixed and total number of organoids and % invasive organoids (determined by morphology) were counted by a researcher blind to the treatment protocol. Kindolor reduced the % invasive organoids.
Kindolor as an Adjunct to Cancer Chemotherapy

• Kindolor may be effective at preventing metastasis.

• Significant reductions in mammary tumor cell metastasis were evident with doses of Kindolor in the range of 20 μM.

• Coupled with Kindolor’s analgesic properties it becomes a perfect adjunct to cancer chemotherapeutic regimens that involve drugs like cisplatin and/or paclitaxel.
Differentiation From the Current Standards of Care

• In addition to relieving neuropathic once it develops, Kindolor prevents the development of chronic pain when given soon after injury

• Low dose Kindolor potentiates the actions of analgesics
  — Combination of Kindolor with analgesics lowers doses of current SOC should help to limit side-effects inherent to the current SOC

• Kindolor has improved tolerability profile vs. SOC
  — No CNS liabilities including:
    — psychiatric / mood disturbances
    — cognitive or motor coordination impairment
    — disturbances in sleep architecture
    — interactions with alcohol
    — abuse / drug dependency
  — Low likelihood of CV, GI, renal or hepatic side effects

• Kindolor is a novel “systems biology” strategy
  — Chronic pain is the result of multiple maladaptations in the body and likely will require a multi-target approach for effective treatment
  — Kindolor, unlike the current SOC and most medications being developed, offers a broad-spectrum approach that targets multiple systems responsible for chronic pain
Kindolor

IND Activities and Clinical Development

Targeting an IND within a year
Clinical Therapeutic Targets

- Painful Diabetic Peripheral Neuropathy
- Post-Herpetic Neuralgia (PHN)
- Chemotherapy –Induced Neuropathy
- Phantom limb pain
- Fibromyalgia
- Mono and polyneuropathies
- Oncology all-comers