

## **Battlefield Pain Control Update: Intranasal Ketamine**

### **Programmatics**

- \$8.0M effort (equally co-funded \$4M DoD , \$4M Industry)
- \$1.5M initial set aside for cognitive performance wedge
- Linked to Army requirements: TRADOC Pamphlet 525-66, FOC-11-05: b(4)(d), Global Casualty Care Management and Evacuation explicitly requires improved drugs to manage pain
- Task Area for Battlefield Pain Control established (March 2002)
- Advanced Technology Demonstration Master Plan Drafted: Nasal Ketamine for Injury Pain Relief on the Battlefield (March 2003)
- Cognitive and Operational Performance Effects of Intranasal Ketamine Integrated Research Team established (June 2004)

### **Needs Statement and Military Relevance**

#### **Need:**

- There exists an Army need to determine if the administration of intranasal ketamine in sufficient doses to grant moderate to severe pain relief elicits cognitive impairment, including hallucinations and other psychotomimetic events

#### **Relevance:**

- Treatment of combat casualties with morphine leads to inability of the soldier to function effectively
- Intranasal ketamine may be an effective analgesic *without* adverse cognitive side effects

### **Goal**

- To demonstrate whether ketamine, applied intranasally as self-medication by the individual Warfighter, can manage moderate to severe pain while allowing the Warfighter to remain cognitively functional
- Operational context includes the potential for pain relief and mission continuation, including effective defense and possible mission accomplishment

### **Studies Completed to Date (detailed below)**

- KET-PK-001 Pharmacokinetics, Dose Proportionality and Absolute Bioavailability of PMI-100 (Intranasal Ketamine) in Healthy Volunteers (N=18)
- KET-001: Randomized, Placebo-Controlled, Double-Blind, Study of the Safety and Efficacy of PMI-100 for the Treatment of Breakthrough Pain in Patients with Chronic Malignant Pain, (N=20)
- KET-002: Randomized, Placebo-Controlled, Double-Blind, Study of the Safety and Efficacy of PMI-100 for the Treatment of Orthopedic Injury Pain in the Emergency Room, (N=40)
- KET-003: Randomized, Placebo-Controlled, Double-Blind, Study of the Safety and Efficacy of 10 mg, 30 mg and 50 mg of PMI-100 for the Treatment of Postoperative Dental Pain, (N=40)
- KET-003B: Randomized, Placebo-Controlled, Double-Blind, Study of the Safety and Efficacy of 2.5 mg, 5 mg and 10 mg of PMI-100 for the Treatment of Postoperative Dental Pain, (N=40)

**Ongoing Studies**

- KET-004: A Randomized, Double-Blind, Crossover-group Pilot Comparison of the Analgesic Efficacy and Safety During Wound Care in Burn Victims of PMI-100 (Intranasal Ketamine HCL) and Placebo Following a Single Dose Administration of Intravenous Morphine, (N=12)<sup>1</sup>
- KET-PK-004 Pharmacokinetics, Dose Equivalence of PMI-100 and PMI-150 in Healthy Volunteers, (N=26) Backup Details

**Funded FY05 Studies**

**In review MRMC, HSRRB**

- KET-PK-005 An Open Label, Randomized, Two-Period, Two-Sequence, Two-Way Crossover, Single Center Study to Assess the Bioequivalence of the Bi-Dose and Multiple Dose Delivery Systems for Intranasal Ketamine in Normal Healthy Adult Volunteers (N=56)

**In review IRB**

- KET-COG-001 Cognitive and Performance Effects of Intravenous Administration of Ketamine in Normal, Healthy Volunteers (N=80)
- KET-COG-002 The Effects of Nasal Ketamine and Placebo on the Performance of Soldier Common Tasks and CANTAB subtasks (N=18)

**Planned FY06 Drug Studies**

- KET-009, as mentioned previously, is the revised study of burn pain at two sites (Shands and Harborview), using a modification of the original protocol such that the single, revised protocol will allow both to conduct the study in accordance with the SOPs in effect at each site. The revisions from KET-004 to KET-009 concern selections of pretreatment medications and doses that were acceptable to the PIs of both sites. (N=12)
- KET-010A, A Single-Dose, Bridging Study Employing the PMI-100 and PMI-150 Formulations (N=60)
- KET-010B, A Multiple-Dose Study Employing Initial Single Doses Of 30 Or 60 mg, Followed By Rescue Doses Of Either 30 Or 60 mg (N = 50)
- KET-005, is a pivotal trial of nasal ketamine for acute postoperative orthopedic pain. The N will be chosen based upon a power analysis using results from KET-010A. If that preliminary trial does not support the validity of this model, we shall select an alternative pain model.

**Planned FY06 Cognitive Studies**

- KET-COG-003 Cognitive Deficits of a Sub Anesthetic Concentration of Ketamine vs Morphine at a Standard Field Dose with the Application of Standardized Painful Stimuli (N=48)
- KET-COG-004 Task Performance and Crew Coordination in a Vehicle Simulator Following Administration of Intranasal Ketamine or IV Morphine (N=18)
- KET-COG-005 Marksmanship Performance, Map-Compass Tasks, and "Shoot-Don't Shoot" Tests of Higher Mental Functioning Following Administration of Intranasal Ketamine or IV Morphine (N=20)

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<sup>1</sup> KET-004 was closed because of a change in SOP in the Brooke Army Medical Center site, that precluded use of ketamine as planned. Accordingly, in consultation with Harborview (Seattle) and Shands (Gainesville), we have modified the burn dressing change protocol so as to accord with the SOPs at both centers. This study is now termed KET-009 described later.

**Backup/Details: Intranasal Ketamine**

**Background: Product profile**

- Optimal dose is 3 to 5 sprays (30 – 50 mg)
- Absolute bioavailability PMI-100 = 35.5%

**Therapeutic Index**

- 15 X difference between analgesic and anesthetic dose
- Analgesic Dose of 50mg PMI-100 ( $50\text{mg} \times 35.5\%$ ) = 18 mg
- Anesthetic Dose of IV Ketamine (Ketalar®) = 280 mg

**Intranasal Ketamine Review**

Pharmacokinetics, Dose Proportionality and Absolute Bioavailability of PMI-100 (Intranasal Ketamine) in Healthy Volunteers, 2 period, cross-over, IV vs. PMI-100 (10, 30, 50 mg)

- $t_{1/2}$  (h) = 5.8
- $T_{\text{max}}$ (h) = 0.42
- Bioavailability 35.3% [90% CI 22.3-55.8]

**Summarized Results from Completed/Ongoing Studies**

Randomized, Placebo-Controlled, Double-Blind, Study of the Safety and Efficacy of PMI-100 for the Treatment of Breakthrough Pain in Patients with Chronic Malignant Pain  
2 period, cross-over, placebo vs. PMI-100 (10 to 50 mg)

- Mean reduction in pain intensity (NPIS) 0 to 60 minutes 2.65 vs. 0.81 ( $p < 0.0001$ )
- Statistically significant  $\geq 40\%$  reduction in pain intensity ( $p = 0.0078$ )
- Use of rescue medication 0% vs. 35% ( $p = 0.0156$ )
- Mean dose 43.5 mg
- Statistically significant reduction in pain intensity at 10 minute timepoint ( $p = 0.0039$ )

Randomized, Placebo-Controlled, Double-Blind, Study of the Safety and Efficacy of PMI-100 for the Treatment of Orthopedic Injury Pain in the Emergency Room. Single dose, parallel group, placebo vs. PMI-100 (10 to 50 mg)

- Mean reduction in pain intensity (VAS) 0 to 60 minutes 27.2 mm vs. 21.7 mm ( $p = 0.3013$ )
- Statistically significant  $\geq 20\%$  reduction in pain intensity ( $p = 0.0078$ )
- Use of rescue medication 10% vs. 35% ( $p = 0.1274$ )
- Mean dose 45.8 mg

Randomized, Placebo-Controlled, Double-Blind, Study of the Safety and Efficacy of 10 mg, 30 mg and 50 mg of PMI-100 for the Treatment of Postoperative Dental Pain. Single dose, parallel group, placebo vs. PMI-100 (10, 30 and 50 mg)

- Statistically significant total pain relief over 3 hours (TOTPAR3) for 10, 30 and 50 mg groups
- Statistically significant  $\geq 40\%$  reduction in pain intensity VAS ( $p = 0.0257$ )
- Rescue meds in first 3 hours 50% vs. 100% ( $p = 0.0325$ )
- Statistically significant reduction in pain intensity at 10 minute 50 mg PMI-100 timepoint ( $p = 0.0084$ )
- Median time to rescue medication 50 mg PMI-100 [139 minutes] and 30 mg PMI-100 [126 minutes]

Randomized, Placebo-Controlled, Double-Blind, Study of the Safety and Efficacy of 2.5 mg, 5 mg and 10 mg of PMI-100 for the Treatment of Postoperative Dental Pain. Single dose, parallel group, placebo vs. PMI-100 (2.5, 5.0 and 10 mg)

- No statistically significant total pain relief over 3 hours (TOTPAR3) for 2.5, 5.0 and 10 mg groups

### **Studies in progress**

Pharmacokinetics, Dose Equivalence of PMI-100 and PMI-150 in Healthy Volunteers

An open label, randomized, four sequence, four-way crossover comparing 30 mg delivered by three (3) sprays of intranasal ketamine (PMI-100) vs. 2 sprays of intranasal ketamine (PMI-150) and 60 mg delivered by 6 sprays of intranasal ketamine (PMI-100) vs. 4 sprays of intranasal ketamine (PMI-150). Twenty-eight (28) healthy volunteers will be randomized to four (4) possible sequence groups with seven (7) patients per sequence group, using a Latin square crossover design. 2 period, cross-over, PMI-150 vs. PMI-100 (30, 60 mg)

Pharmacokinetics, Dose Equivalence of PMI-150 (BD) and PMI-150 (MD) in Healthy

Volunteers. An open label, randomized, two-period, two-sequence, two-way crossover study comparing 15 mg of PMI-150 delivered by the bi-dose nasal delivery system versus the multiple dose nasal delivery system or 75 mg of PMI-150 delivered by the bi-dose nasal delivery system versus the multiple dose nasal delivery system. Fifty-six healthy volunteers will be randomized to four sequence groups with 14 subjects per sequence group (12 evaluable subjects per group).