# A Multicenter, Open-Label, Phase 1b Study to Assess the Safety and Define the Maximally Tolerated Dose of Epidural Resiniferatoxin (RTX) Injection for Treatment of Intractable Pain Associated with Cancer

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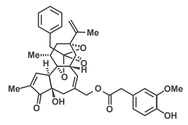
## Introduction

- From Euphorbia (cactus-like) plants
- Ultrapotent agonist of TRPV1 receptor[1]
- RTX vs. capsaicin
  - RTX ~18 Billion Scoville units
  - Capsaicin ~16 Million Scoville Units




- Highly specific: affects only TRPV1 expressing nerves (Aδ and C fibers)
- RTX activates TRPV1 receptor inducing influx of calcium, leading to lysis of pain-sensory neurons
- Cancer-related pain, reported by more than 70% of patients, is one of the most common and troublesome symptoms affecting patients with cancer. Despite the availability of effective treatments, cancer-related pain may be inadequately controlled in up to 50% of patients.[2]

## Methods

- Phase 1b, open-label, single-dose RTX, 3 + 3 dose escalation design
- Subjects with intractable chronic pain (NPRS worst pain ≥ 6) due to advanced cancer
- Dose levels: 0.4, 1, 2, 4, 8, 15 mcg in 3 mL saline
  - First 2 dose levels may advance after first subject dosed if no DLTs
- Administered epidurally as interlaminar injection at midline L2-L3, L3-L4, L4-L5, L5-S1, or via caudal catheter L5 to S4 under anesthesia

## Demographics & Baseline Characteristics

| Demographics, Baseline Characteristics | RTX N=14 |
|---|---|
| Female, Male: n (%) | 9 (64.3%) |
| | 5 (35.7%) |
| Age, Median (min, max) | 58.5 (40, 82) |
| Baseline Worst NPRS, Mean (SD) | 7.8 (1.3) |
| Baseline Average NPRS, Mean (SD) | 6.9 (1.7) |
| Baseline Worst NPRS <6: n (%) | 1 (7.1%) |
| Baseline Worst NPRS ≥ 6, <8: n (%) | 4 (28.6%) |
| Baseline Worst NPRS ≥ 8: n (%) | 9 (64.3%) |

| Cancer Diagnosis | N=14 |
|---|---|
| Breast | 2 (14.3%) |
| Lung | 2 (14.3%) |
| Multiple Myeloma | 2 (14.3%) |
| Rectal | 2 (14.3%) |
| Renal cell | 2 (14.3%) |
| Gastrointestinal Stromal Tumor | 1 (7.1%) |
| Endometrial | 1 (7.1%) |
| Large-B-cell Lymphoma | 1 (7.1%) |
| Myxoid Liposarcoma | 1 (7.1%) |

1. Moran MM, Szallasi A. Targeting nociceptive transient receptor potential channels to treat chronic pain: current state of the field. *Br J Ph*, 2018, V175, 2185-2203.
2. Neufeld NJ, Einahal SM, Alvarez RH. Cancer pain: a review of epidemiology, clinical quality and value impact. *Future Oncology*, 2017, V13, 833-841.

## Results

### Safety

- No DLTs were reported.
- Serious AEs were attributed to progression of underlying cancer.
- Most common treatment related AE was transient procedural pain which sometimes was described as burning sensation in lower extremities which diminished over several hours and disappeared afterwards.

| Treatment-Emergent Adverse Events Related to RTX | | | |
|---|---|---|---|
| TEAE | Severity | SAE | RTX Treated (N=14) |
| Procedural pain | Moderate | No | 7 (50.0%) |
| Back Pain | Moderate | No | 1 (7.1%) |
| Burning sensation | Mild | No | 1 (7.1%) |
| Bradycardia | Mild | No | 1 (7.1%) |
| Hypertension | Mild | No | 1 (7.1%) |
| Increased blood pressure | Moderate | No | 1 (7.1%) |
| Nausea | Mild | No | 1 (7.1%) |

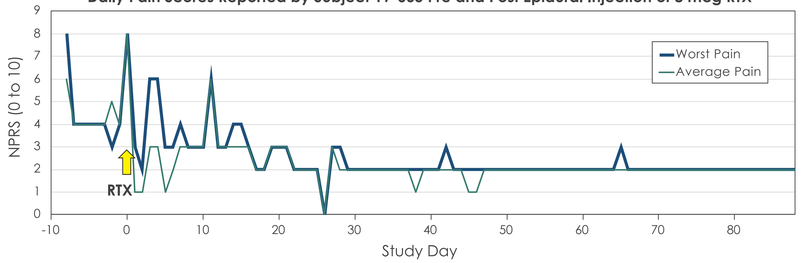
### Pharmacokinetics

- Only 1 of 14 subjects at any dose level had detectable (>50 pg/mL) RTX in plasma following injection.
  - Dose was 15 mcg; plasma levels peaked at 97 pg/mL RTX at 0.5 hour and was not detectable by 2 hours after injection.

### Efficacy

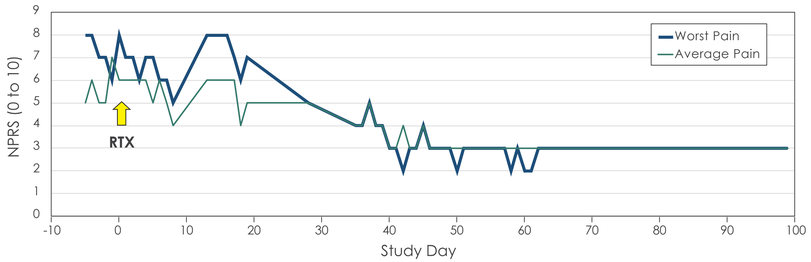
Positive outcomes were observed in 3 subjects at higher doses of RTX.

- 58 yo woman with gastrointestinal stromal tumor with severe target pain in lower back; received 8 mcg RTX; reported a decrease in pain scores (NPRS) and discontinued daily use of Tramadol.

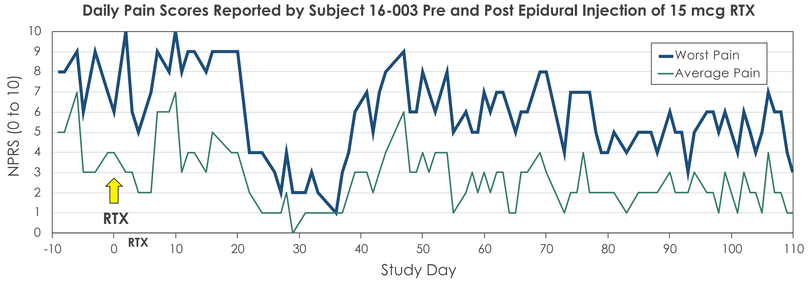



### Efficacy (cont)

- 62 yo man with rectal cancer with severe rectum and tailbone pain; received 15 mcg RTX; noted significant improvement in pain, physical strength, mood, and appetite with NPRS pain scores reduced from 7 to 8/10 to 3/10.




- 57 yo man with multiple myeloma and severe low back pain, received 15 mcg RTX; reported only mild pain in this target area post RTX injection




## Conclusion

- Resiniferatoxin (RTX) was tolerable at all doses tested (with concomitant analgesics administered).
- PK data showed undetectable drug in plasma in 13/14 subjects
- A dose-dependent decrease in pain scores was detected.
- RTX has the potential to alleviate severe pain associated with cancer.