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

SS Nedeljkovic[1], S Narang[1], E Rickerson[1], RC Levitt[2], DB Horn[2], DJ Patin[2], N Albores-Ibarra[3], A Nahama[5], T Zhao[5], P Bharathi[5], M Luchi[5], H Minkowitz[3], D Solanki[3], D Leiman[3,4]

[1]Brigham and Women's Hosp., Boston, MA; [2]Univ. of Miami, Miami, FL; [3]HD Res., Houston, TX; [4]Univ. of Texas at Houston, Dept of Surgery, Houston, TX; [5]Sorrento Therapeutics, Inc., San Diego, CA

Sorrento Therapeutics, Inc.
4955 Directors Place
San Diego, CA 92121

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Introduction

- Derived from Euphorbia (cactus-like plant).
- 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, resulting in lysis of pain-sensory neurons.
- Cancer-related pain is one of the most common and troublesome symptoms and is reported by more than 70% of 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, 25 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=17
Female: n (%)	11 (64.7%)
Male: n (%)	6 (35.3%)
Age, Median (min, max)	58.0 (28, 82)
Baseline Worst NPRS, Mean (SD)	7.8 (1.26)
Baseline Average NPRS, Mean (SD)	6.8 (1.66)
Baseline Worst NPRS <6: n (%)	1 (5.9%)
Baseline Worst NPRS ≥ 6, <8: n (%)	8 (47.1%)
Baseline Worst NPRS ≥ 8: n (%)	8 (47.1%)

Cancer Diagnosis	n=17
Breast	2 (11.8%)
Lung	2 (11.8%)
Multiple Myeloma	2 (11.8%)
Rectal	2 (11.8%)
Renal cell	2 (11.8%)
Bladder	1 (5.9%)
Endometrial	1 (5.9%)
Gastrointestinal Stromal Tumor	1 (5.9%)
Large-B-cell Lymphoma	1 (5.9%)
Myxoid Liposarcoma	1 (5.9%)
Neuroblastoma	1 (5.9%)
Rectosigmoid	1 (5.9%)

Results

Safety

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

Safety – Treatment Emergent Adverse Events		
TEAE	Severity	RTX Treated (n=17)
Procedural pain	Moderate	8 (47.1%)
Back Pain	Moderate	1 (5.8%)
Burning sensation	Mild	1 (5.8%)
Bradycardia	Mild	1 (5.8%)
Hypertension	Mild	1 (5.8%)
Increased blood pressure	Moderate	1 (5.8%)
Nausea	Mild	1 (5.8%)
Paraesthesia	Mild	1 (5.8%)
Groin pain	Mild	1 (5.8%)

Pharmacokinetics

- Only 2 of 17 subjects at any dose level had detectable (>50 pg/mL) RTX in plasma following injection.
  - Dose at 15 mcg; plasma level peaked at 97 pg/mL RTX at 0.5 hour and was not detectable by 2 hours after injection.
  - Dose at 25 mcg; plasma level peaked at 76 pg/mL RTX at 1 hour and was not detectable at other time points.

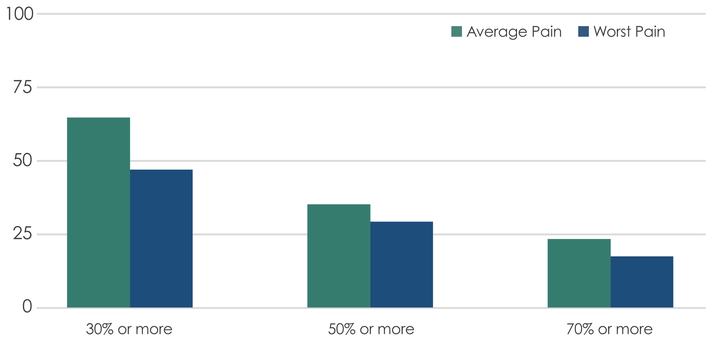
Efficacy

- Clinical efficacy assessed at 3 levels: 30%, 50%, and 70% decrease in pain from baseline NPRS score.
- Dose-response relationship observed for majority of responders at 15 mcg and 25 mcg levels.
- Eleven of 17 subjects achieved a 30% decrease in pain using NPRS scores.

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.

Efficacy				
Percent Decrease in Pain from Baseline	Average Pain		Worst Pain	
30% NPRS reduction	15 mcg	100%	15 mcg	66.7%
	25 mcg	66.7%	25 mcg	66.7%
	All Dose Levels	64.7%	All Dose Levels	47.1%
50% NPRS reduction	15 mcg	33.3%	15 mcg	66.7%
	25 mcg	66.7%	25 mcg	33.3%
	All Dose Levels	35.3%	All Dose Levels	29.4%
70% NPRS reduction	15 mcg	33.3%	15 mcg	33.3%
	25 mcg	33.3%	25 mcg	33.3%
	All Dose Levels	23.5%	All Dose Levels	17.6%

Percent Decrease in Pain from Baseline*



*Day 90 results for all RTX doses pooled

Conclusion

Resiniferatoxin (RTX) has the potential to alleviate severe pain in patients who have intractable cancer pain.

- RTX was tolerable at all doses tested (with concomitant analgesics administered for procedural pain on Day 1).
- PK data showed undetectable drug in plasma in 15/17 subjects.
- A dose-dependent decrease in pain scores was detected.