RespireRx Pharmaceuticals Inc

Antagonism of Remifentanil-Induced Respiratory Depression by CX1739 in Two Clinical Models of Opioid Induced Respiratory Depression (OIRD)

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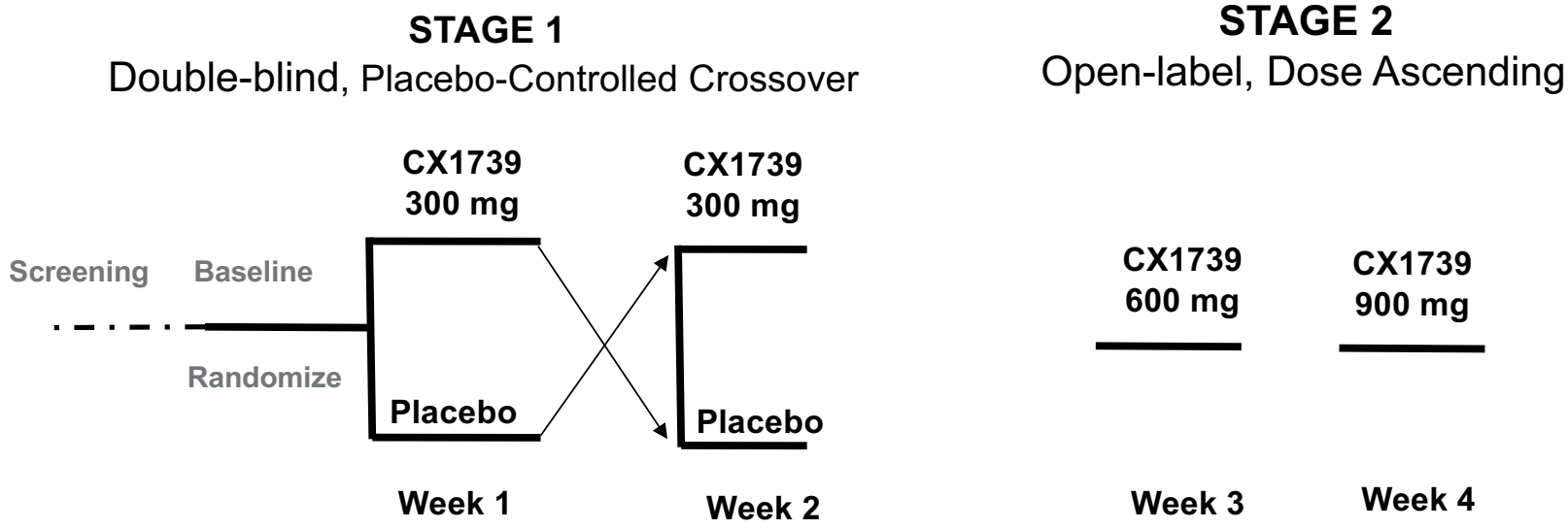
Opioid analgesics are now the most commonly prescribed class of medications in the United States, where chronic pain is estimated to affect around 68 million people each year. In 2014 alone, U.S. retail pharmacies dispensed 245 million prescriptions for opioid pain relievers. Opioids are useful and effective analgesics but produce several unwanted side effects, including episodes of life-threatening respiratory depression, which resulted in over 30,000 deaths in 2014. For this reason, an unmet medical need exists for an agent that can antagonize opioid-induced respiratory depression without compromising the analgesic effects of opioids.

We herein describe the results of a phase IIa clinical trial that evaluated the ability of CX1739 to overcome the respiratory depression induced by the powerful, yet short-acting opioid, remifentanil in two models of opioid use: a. REMI-Bolus evaluated respiratory parameters in an opioid overdose model, using a bolus of remifentanil (1 mcg/kg) to achieve significant respiratory depression; b. REMI-Infusion evaluated respiratory, pain, and pupilometry parameters using an infusion of remifentanil at a steady state blood concentration of 2 ng/ml to achieve approximately 40 - 50% respiratory depression as a model of sub-acute, post-surgical intravenous opioid treatment as well as chronic oral opioid treatment for chronic pain. The results of the REMI-Bolus analysis demonstrate that CX1739 does not prevent the rapid respiratory depression that occurs after intravenous, bolus injection of remifentanil. The results of the REMI-Infusion analysis demonstrate that, compared to placebo, an acute dose of CX1739 (300 mg or 900 mg) significantly reduces OIRD under steady-state opioid concentrations. The remifentanil effects on analgesia, pupilometry and bispectral index were not altered. Administration of CX1739 at an acute dose up to 900 mg was safe and comparable to placebo.

Overall Study Design: CX1739 vs. Placebo in Combination with the Opioid Remifentanil



Randomized, Blinded, Placebo-controlled, Cross-Over with Acute Dose Escalation of CX1739
Study Population 1: Placebo vs. 300 mg CX1739 (n=19; Completed Visits 1 and 2; Blinded)
Study Population 2: Placebo vs. 300 mg, 600 mg, and 900mg CX1739 (n=17; completed 4 visits)

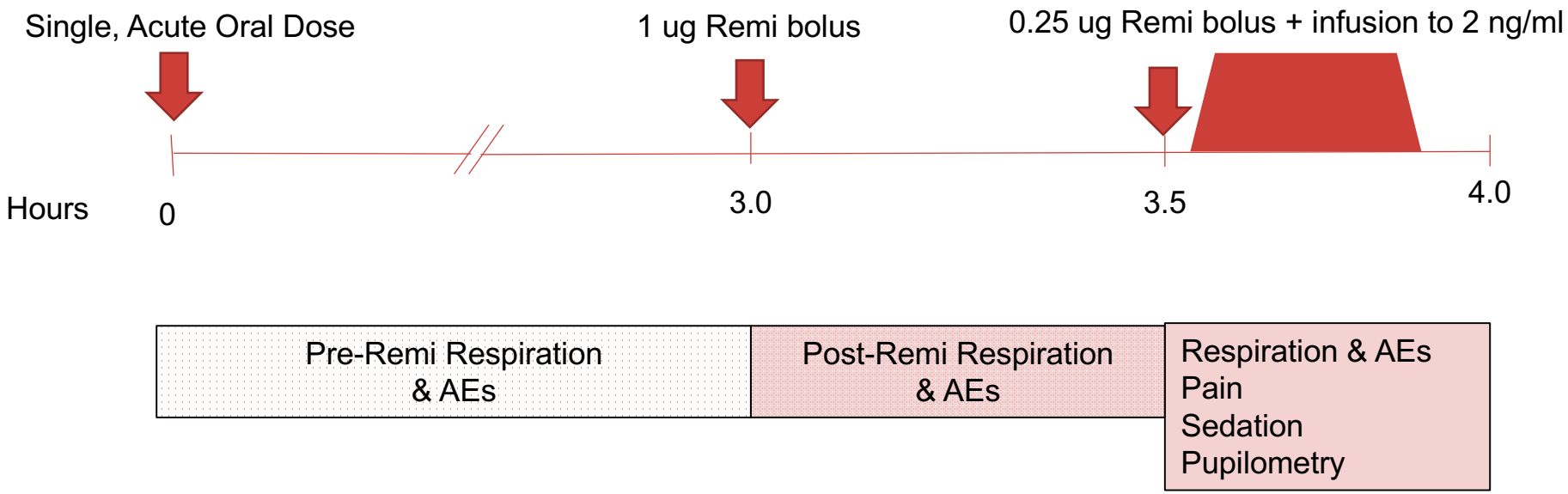
Remifentanil Dosing
4 Weekly visits two protocols for remifentanil administration (REMI Infusion and REMI Bolus)
REMI Infusion – Model of post-surgical pain management and chronic opioid use
REMI Bolus – Model of IV drug overdose prevention and rescue

Weekly Acute Dose Testing of CX1739 vs Remifentanil: Bolus and Infusion Models of Opioid Use

CX1739/Placebo
0, 300, 600, 900 mg
3-Hr Preadministration
For Cmax

REMI-Bolus
Single, acute bolus injection
Model of acute overdose

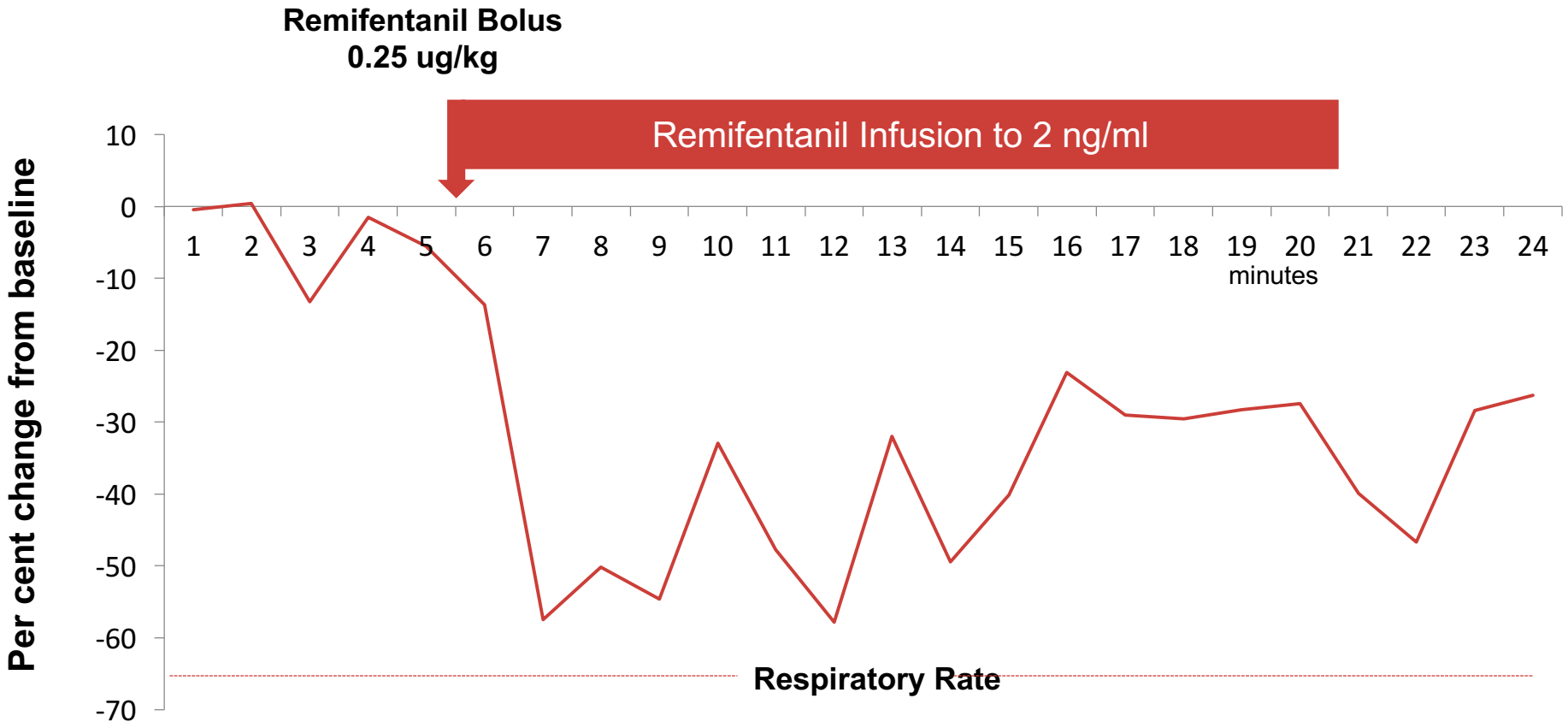
REMI-Infusion
Continuous infusion
Model of chronic use



Endpoint Measures
REMI Bolus: Effect of CX1739 on % change from baseline for RR, TV, and MV & Time to respiratory recovery following remifentanil-induced RD
REMI Infusion: Effect of CX1739 on opioid induced respiratory depression (% change from baseline for RR, TV, and MV) at a steady-state dose of remifentanil (2ng/ml)

REMI-Infusion Protocol: A Model of Chronic Opioid Use for Pain Management

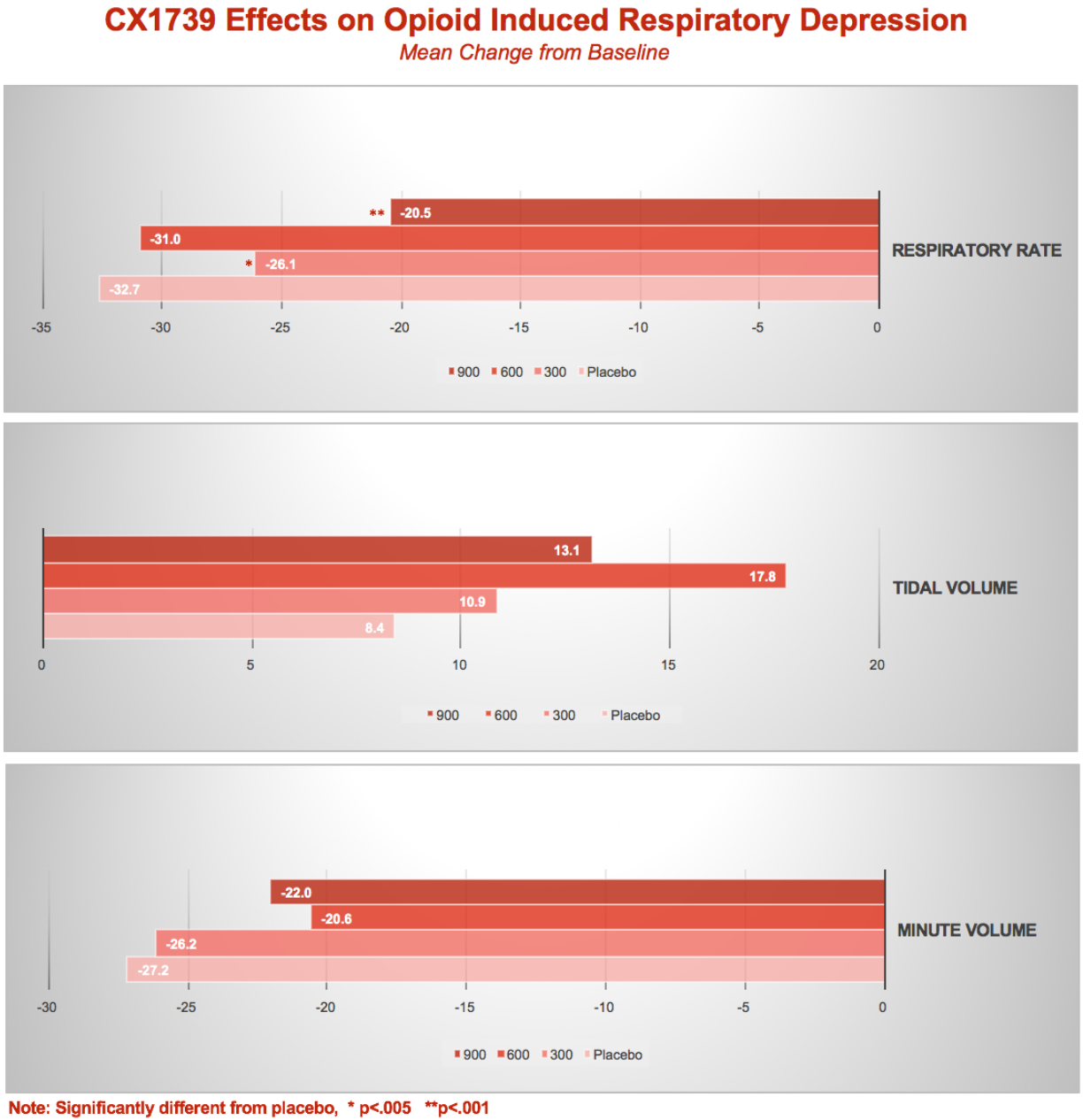
Effects of Remifentanil on Respiratory Rate (RR) in Representative Subject



Clinical Outcome Measures:

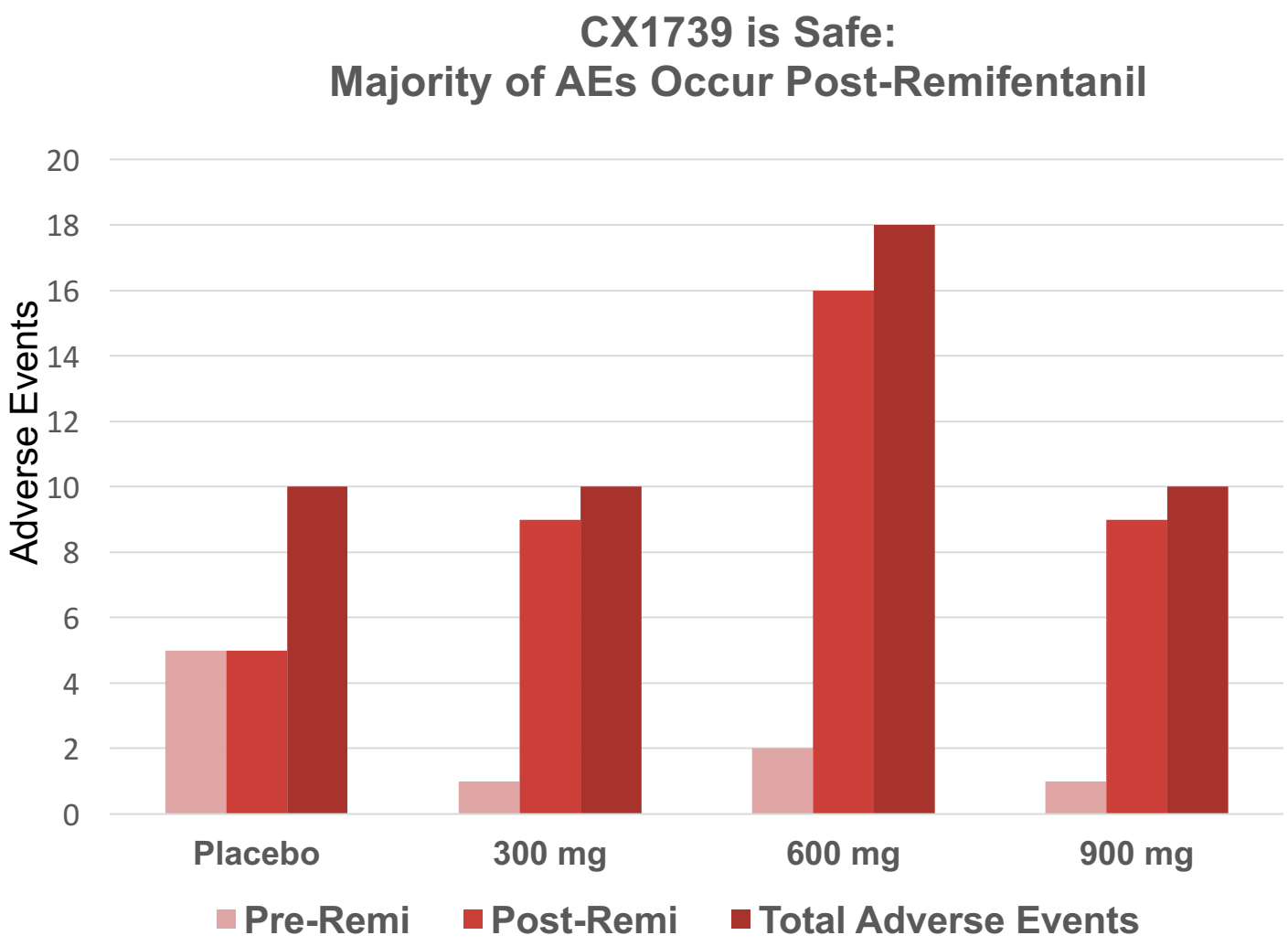
- Respiration – Expiron Respiratory Motion® (RR, TV, MV)
- Pain – Heat & Electrical Stimulation
- Sedation – BIS Monitoring

CX1739 Antagonizes the Respiratory Depressive Effects of Remifentanil



Note: Significantly different from placebo, * p<.005 **p<.001

CX1739 is Safe and Well Tolerated with No SAEs

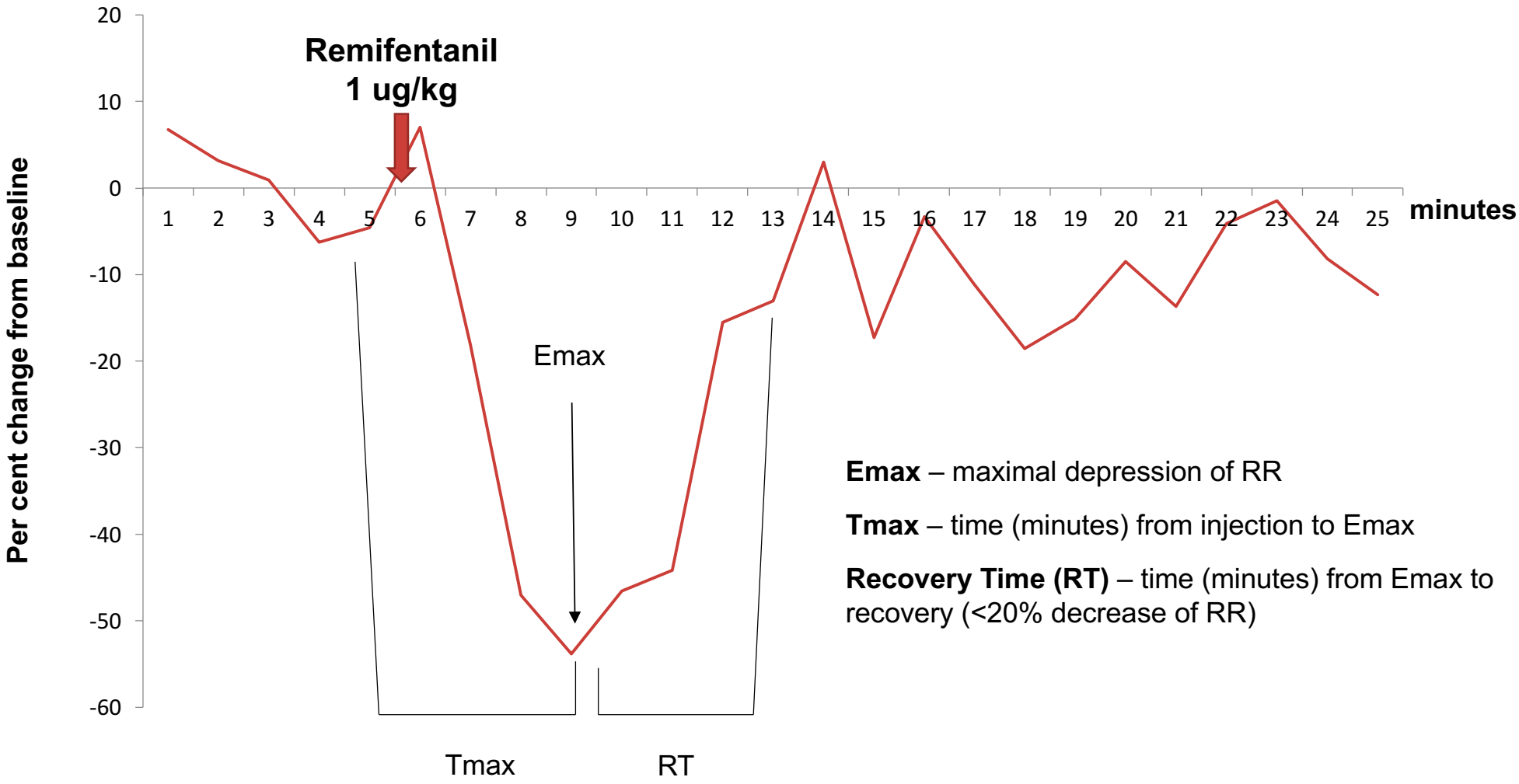


Adverse Events

- 38 of 48 AEs occurred after remifentanil
- Pre-remifentanil Placebo had as many AEs as all doses of CX1739 combined
- Most frequent AEs were nausea, vomiting, headache and dizziness, all of which are common side effects of opioids

REMI-Bolus Protocol: A Model of Intravenous Opioid Overdose

Effects of Remifentanil on Respiratory Rate (RRT) in Representative Subject



Emax – maximal depression of RR

Tmax – time (minutes) from injection to Emax

Recovery Time (RT) – time (minutes) from Emax to recovery (<20% decrease of RR)

Similar measurements were made for Tidal Volume (TV) and Minute Volume (MV)

CX1739 Does Not Prevent the Initial Drop in Respiratory Depression In the IV Opioid Overdose Challenge

		CX1739		
	Placebo N = 17	300 mg N = 17	600 mg N = 17	900 mg N = 17
Emax* (%)	-65.1 +/-23.0	-61.9 +/-26.7	-75.8 +/-22.6	-72.6 +/-24.3
Tmax* (minutes)	5.8 +/-5.1	4.5 +/-3.7	3.2 +/-2.6	3.4 +/-3.1
Recovery time* (minutes))	7.6 +/-10.3	5.4 +/-3.9	5.7 +/-3.5	5.9 +/-4.8
	* Mean +/- SD			

Additional research is warranted to explore the effects of CX1739 on Emax and RT

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Conclusion: CX1739 Has Potential Clinical Utility for the Treatment of Opioid Induced Respiratory Depression

- CX1739 significantly antagonized remifentanil induced respiratory depression during REMI-Infusion, a model of opioid induced respiratory depression (OIRD).
- CX1739 is safe and well-tolerated, with no serious adverse events reported in the trial.
- Though CX1739 antagonized OIRD, pain control was maintained, as CX1739 did not significantly alter analgesia or sedation produced by remifentanil.
- CX1739 did not antagonize respiratory depression during REMI-Bolus, a model of acute opioid overdose.
- These positive results warrant additional clinical trials of CX1739:
  - Central sleep apnea (CSA) in patients taking chronic oral opioids
  - Post-operative pain management concomitant with opioid IV infusions
  - Prevention of OIRD In patients taking chronic oral opioids for pain management
  - Extension of OIRD recovery after naloxone rescue