

# A Double-Blind, Placebo-Controlled Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single, Escalating Oral Doses of JDTic

Jeffrey J Buda<sup>1</sup>, FI Carroll<sup>2</sup>, Thomas R Kosten<sup>3</sup>, Dennis Swearingen<sup>4</sup> and Bradford B Walters<sup>\*2</sup>

<sup>1</sup>RTI Health Solutions, Research Triangle Park, NC, USA; <sup>2</sup>RTI International, Research Triangle Park, NC, USA; <sup>3</sup>Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX, USA; <sup>4</sup>Celerion, Tempe, AZ, USA

Animal studies suggest that kappa opioid receptor antagonists (KORAn) potentially could treat a wide variety of addictive and depressive disorders. We assessed the KORAn JDTic for safety, tolerability, and pharmacokinetics in a double-blind, placebo-controlled, randomized trial evaluating single oral doses in healthy adult males. Predose and postdose safety assessments included orthostatic vital signs; 6-lead continuous telemetry monitoring (approximately 16 h predose to 24 h postdose); 12-lead electrocardiograms (ECGs); clinical chemistry, hematology, coagulation, and urinalysis; psychomotor functioning (using the Wayne Saccadic Fixator (WSF)); and adverse events. As a potential indicator of JDTic effects on affect, the POMS Standard instrument was administered predose and daily postdose Days 1–6. At 1 mg, 2 of the 6 JDTic (and 0/6 placebo) subjects experienced a single, asymptomatic event of multiple beats of nonsustained ventricular tachycardia (NSVT). Their events were temporally similar with respect to time postdose (and the postdose timing of an NSVT event in a monkey). These events triggered a study stopping rule. No differences were observed between the placebo and JDTic subjects with respect to clinical chemistry, hematology, coagulation, urinalysis, orthostatic vital signs, WSF, or 12-lead ECG parameters. Plasma JDTic levels were below the lower limit of quantitation (0.1 nM) in all subjects. There were no significant differences in POMS scores between the placebo and JDTic groups. Although the evidence is circumstantial, it suggests that NSVT is a potential JDTic toxicity in humans. Given the therapeutic potential of KORAn, further investigation is needed to determine whether a significant JDTic human cardiac effect indeed exists, and if so, whether it is specific to JDTic or represents a KORAn class effect.

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## INTRODUCTION

The kappa opioid receptor (KOR) and its endogenous ligand dynorphin are enriched in brain regions involved in stress response, and potential clinical utility for KOR antagonists (KORAn) has been shown in depression and substance abuse (Carroll and Carlezon, 2013). JDTic is a potent and selective KORAn (Thomas *et al*, 2003) that in preclinical models shows antidepressant and anxiolytic activity and reduces the signs of nicotine withdrawal, the stress-induced reinstatement of cocaine-reinforced behavior, and manifestations of alcohol abuse (Carroll and Dolle, 2014). KORAn are a drug class of considerable pharmaceutical interest, and RTI International intended to develop JDTic for several indications. This article reports the results of the first-in-human safety study.

Kappa-active compounds also have cardiovascular effects; however, results are mixed. In most rat studies, kappa

opioid receptor agonists (KORAg) are cardioprotective (eg, Jaiswal *et al*, 2010; Zhou *et al*, 2001), reduce arrhythmias (eg, Jin-Cheng *et al*, 2008; Lishmanov *et al*, 2007; Peart *et al*, 2004; Xiu *et al*, 2013), have positive inotropic effects (eg, Pyle *et al*, 2001), and are a component of ischemic preconditioning (Yu *et al*, 1999; Zatta *et al*, 2008). Consequently, KORAn could have negative effects. One study reported that highly selective KORAn activate c-Jun N-terminal kinase (JNK; Bruchas *et al*, 2007). In another study, lipopolysaccharide activation of JNK caused disruption of fatty acid oxidation by a human ventricular-derived cardiomyocyte cell line and caused cardiac dysfunction in C57BL/6 mice (Drosatos *et al*, 2011). However, in dogs (Hartlage *et al*, 2006) and swine (Coles *et al*, 2003), KORAn are cardioprotective. Also, negative inotropic (Ventura *et al*, 1992) and pro-arrhythmic (Bian *et al*, 1998) effects of U-50,488H and cardioprotective effects of nor-BNI (Liu *et al*, 2005) are described in rats.

Biopsied human ventricular myocytes contain dynorphin (Ationu *et al*, 1993), and surgical specimens of human atrial tissue (Lendeckel *et al*, 2005) and pooled human heart extracts (Peng *et al*, 2012) contain KOR mRNA. In human hearts, there are KOR immunoreactive fine nerve fibers, cardiomyocytes, and cells resembling intrinsic

\*Correspondence: Dr BB Walters, RTI International, 3040 E. Cornwallis Road, P.O. Box 12194, Research Triangle Park, NC 27709-2154, USA, Tel: +1 919 316 3509, Fax: +1 919 541 1275, E-mail: bwalters@rti.org  
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cardiac adrenergic cells (Sobanski *et al*, 2014), consistent with rabbit cardiomyocyte immunoprecipitation studies (Surendra *et al*, 2013). The KORAg U-50,488H has negative inotropic effects on isolated human right atrial strips not antagonized by the selective KORAN nor-BNI or the broader-acting naloxone (Lobell and Laorden, 1995). Similarly, U-50,488H has effects on transient outward  $K^+$  and ultrarapid delayed rectifier  $K^+$  currents in human pediatric atrial myocytes that are not antagonized by nor-BNI or naloxone (Xiao *et al*, 2003). However, in human subjects undergoing angioplasty, the acute ischemic preconditioning effect of the first of a pair of balloon occlusions was abolished by naloxone (Tomai *et al*, 1999). Ventricular tachycardia is listed under 'Precautions' and 'Adverse Reactions' in the product insert for naloxone (Hospira, 2007) and is described in case reports (eg, Hunter, 2005). In the first-in-human study of the KORAN LY2456302 (Lowe *et al*, 2014, p. 6), 'a 5-beat ventricular tachycardia occurring approximately 8 h after receiving a single 25-mg dose' was observed in 1 of the 21 subjects (5%) receiving the drug, which does not activate JNK (Melief *et al*, 2011).

Nonclinical studies (data on file, RTI International, Research Triangle Park, NC) identified potential JD<sub>Tic</sub> electrocardiogram (ECG) toxicities but at a human equivalent dose (HED) of >6000 mg and plasma concentrations >920 nM. Review of the first 24 h of ECG following a 200 mg/kg intragastric dose of JD<sub>Tic</sub> (HED of 4500 mg) revealed one of the six cynomolgus monkeys (17%) had three ventricular premature complexes in a row (by definition, nonsustained ventricular tachycardia (NSVT)),

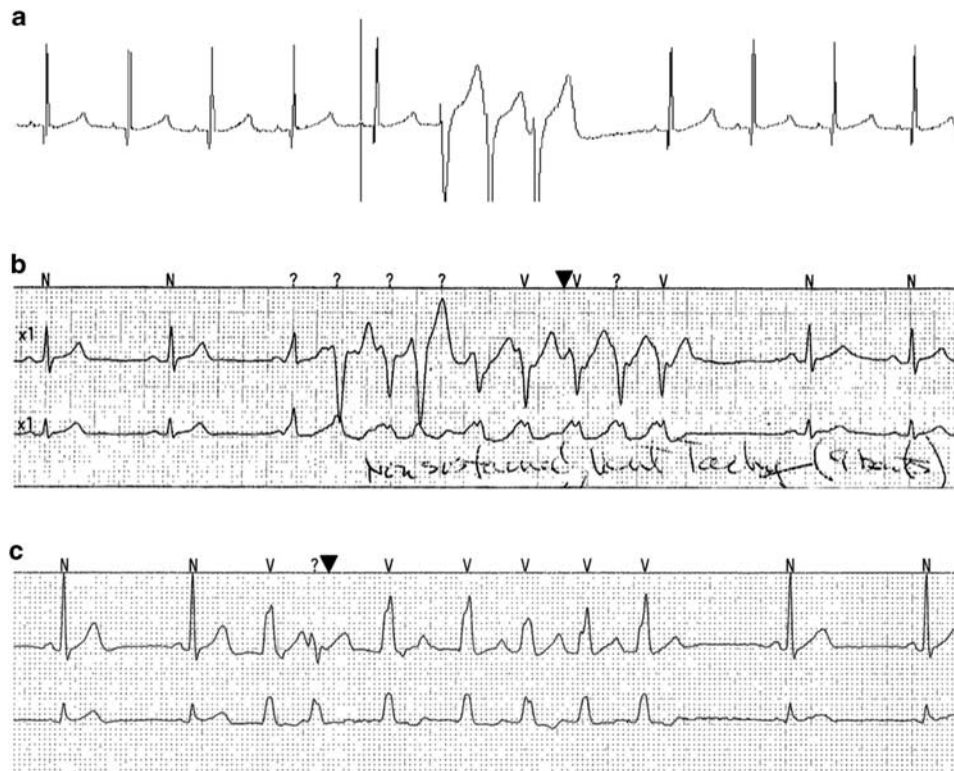
at 11 h 51 min postdose (Figure 1a). NSVT in cynomolgus monkeys can be an incidental finding; 16- to 24-h Holter monitoring of a colony of 62 monkeys revealed ventricular tachycardia (VT) in 8 (13%) (Macallum and Houston, 1993). Asymptomatic NSVT can be observed in humans (cf. Min *et al*, 2010). NSVT prevalence in normal, healthy males is described in four publications using qualitatively different populations (eg, inclusion of females, significantly higher median age), with estimates in the range of 2–3.2% (Bjerregaard, 1982; Brodsky *et al*, 1977; Clarke *et al*, 1976; Hinkle *et al*, 1969).

Following the human trial, a preliminary analysis of JD<sub>Tic</sub> effects in human iPSC cardiomyocyte cultures (approach described by Guo *et al*, 2011) estimated that the concentration at which >20% of the spontaneous beats were arrhythmic was between 2 and 20 nM (Supplementary Figure S1). These concentrations are well below the IC<sub>50</sub> values observed for hERG channel, human cardiac sodium channel, and guinea pig L-type calcium channel (5000 nM) (data on file, RTI).

## SUBJECTS AND METHODS

### Study Design

The JD<sub>Tic</sub>-001 study was a single-center, double-blind, placebo-controlled, randomized clinical trial to evaluate the safety, tolerability, and pharmacokinetics (PK) of single, escalating oral doses of JD<sub>Tic</sub> (1, 3, and 10 mg) in healthy male subjects, in three separate cohorts using a semiadap-



**Figure 1** Nonsustained ventricular tachycardia (NSVT) in preclinical and clinical subjects. (a) 3-Beat NSVT in male cynomolgus monkey 11.8 h after 200 mg/kg intragastric JD<sub>Tic</sub> (timescale not available). (b) 9-Beat NSVT in male human subject 13.5 h after 1 mg oral JD<sub>Tic</sub> (the smallest grid boxes represent 0.04 s). (c) 7-Beat NSVT in male human subject 11.5 h after 1 mg oral JD<sub>Tic</sub> (same timescale as in panel (b)).

tive dosing plan (cohorts 1 and 2 comprised four subjects and cohort 3 comprised eight subjects, in each case randomized 3:1 JD<sub>T</sub>ic:placebo). Prior to dosing a subsequent cohort, all safety and PK data were reviewed by a Safety Review Team (SRT) as guided by a Data and Safety Monitoring Plan (DSMP). If adverse events (AEs) considered to be at least possibly related to study medication occurred during the first two cohorts, an additional four subjects were dosed at that same dose level, unless otherwise determined by the SRT. A final amendment put in place after the initial eight subjects were dosed stipulated that if AEs requiring study termination occurred during an eight-subject cohort, an additional four blinded subjects would be dosed with placebo; consequently, this portion is single blind.

DSMP stopping rules included typical criteria for serious adverse events (SAEs) and adverse events of specific interest (AESI) (eg, terminating the study if  $\geq 25\%$  of a dosing cohort experienced a possibly or definitely drug-related AESI, such as NSVT), as well as limitations on JD<sub>T</sub>ic plasma maximum concentration ( $C_{max}$ ) and area under the curve from zero to infinity ( $AUC_{0-\infty}$ ). The starting dose in the trial, 1 mg, was predicted to result in a maximum plasma concentration of 0.04 nM (below the lower level of quantitation, 0.1 nM); this was reduced from a proposed 3 mg starting dose, in response to a Food and Drug Administration clinical hold. Also in response, protocol ECG exclusion criteria were made even more restrictive than normal (eg, PR interval  $> 180$  ms, QTcB interval  $> 420$  ms), and telemetry was expanded to begin the night before dosing and to continue for 24 h postdose.

Potential subjects presented to the clinic within 14 days of their intended dose date to undergo a battery of screening assessments. Eligible subjects came to the clinic the day before dosing for eligibility reconfirmation. Subjects remained in the clinic that night and for 6 days postdose for safety assessments and timed blood and urine collections. If there were no ongoing safety issues on Day 6, subjects were sent home from the clinic and they returned 14 days later for a follow-up safety assessment. Subjects were then discharged from the study.

This study was approved by the clinical site's Institutional Review Board and conducted in accordance with the International Conference on Harmonisation E6 Consolidated Guidance for Good Clinical Practice (1996), the US Code of Federal Regulations 21 parts 50 and 56, and the ethical principles of the Declaration of Helsinki (as amended in 1996). It was performed at Celerion in Tempe, AZ, and is reported at ClinicalTrials.gov (NCT01431586).

## Participants

**Inclusion criteria.** Subjects were healthy males, 18–50 years,  $\geq 50$  kg in weight, body mass index (BMI) 18–30 kg/m<sup>2</sup>, with normal vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate, oral temperature), a negative prestudy drug screen (alcohol, cannabinoids, amphetamines, benzodiazepines, cocaine, opioids, phencyclidine, barbiturates, cotinine), no history of use of illicit drugs or other substances of abuse within 12 months of the screening visit, no tobacco use for  $\geq 90$  days prior to screening, and no history of cardiovascular disease. Routine 12-lead ECG at screening

(a 10-s single-lead rhythm strip and approximately 2.5-s samples of each lead) had to be without clinically significant abnormalities, as did laboratory analyses of hematology (hemoglobin, hematocrit, reticulocyte count, red blood cells, red blood cell indices, white blood cells, white blood cell differential), chemistry (aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, serum troponin I, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, creatine kinase, lactate dehydrogenase, uric acid, total protein, globulin, cholesterol, triglycerides, sodium, potassium, calcium, chloride, phosphorus), coagulation (prothrombin time, activated partial thromboplastin time), urinalysis (specific gravity, pH, bilirubin, nitrite, urobilinogen, glucose, protein, blood, leukocytes, ketones, microscopic examination), and serology (HIV, hepatitis B surface antigen, hepatitis C antibodies).

**Exclusion criteria.** Subjects were excluded for a history or evidence of hepatic, gastrointestinal, renal, respiratory, ophthalmic, cardiovascular, hematological, endocrine/metabolic, neurological, immunological, oncological, or psychiatric illness or significant abnormalities, or any other conditions or surgical interventions known to interfere with the absorption, distribution, metabolism, or excretion of drugs. Subjects were excluded for any active infection. Consumption of alcohol within 48 h of screening or clinic admission; of caffeine-containing beverages within 72 h of clinic admission; or of grapefruit or grapefruit-, poppy seed-, or quinine-containing substances within 14 days of clinic admission were exclusionary. Subjects were excluded for any clinically significant ECG finding prior to dosing (including bundle branch blocks, second- or third-degree heart block, arrhythmia other than respiratory sinus arrhythmia, or multiple premature atrial contractions or premature ventricular contractions but with the exception of nonclinically significant unifocal premature ventricular contractions), presence or history of early cardiac repolarization, or a history or family history of QT prolongation or arrhythmia. ECG parameters outside the following ranges were also exclusionary: heart rate 55–100, PR interval 120–180 ms, QRS duration 70–100 ms, QTcB interval  $\leq 420$  ms.

## Safety and Tolerability End Points

**Observational.** Orthostatic vital signs were obtained predose and at 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, and 120 h postdose, as well as at 14 days postdose follow-up. Body weight was measured on admission to the clinic, at 48 and 120 h postdose, and at 14 days postdose follow-up. Physical examinations of all major organ systems (including neurological examination) were performed at admission, at 120 h postdose, and at 14 days postdose follow-up. AEs were monitored from dosing until 14 days postdose or resolution, whichever was longer. Psychomotor function was evaluated with the Wayne Saccadic Fixator (WSF; Wayne Engineering, Skokie, IL) on admission and at 120 h postdose.

**Electrocardiogram.** 6-Lead ECG telemetry was monitored from admission (approximately 16 h predose) until 24 h postdose. Supine, standard 12-lead ECGs (a 10-s single-lead rhythm strip and approximately 2.5-s tracings of each lead)



were obtained predose; at 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, and 120 h postdose; and at 14 days postdose follow-up.

**Clinical laboratory.** Urine for urinalysis and fasted blood samples for chemistry, hematology, and coagulation were obtained on admission, at 48 and 120 h postdose, and at 14 days postdose follow-up.

### Pharmacokinetics

Blood samples were obtained at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 30, 36, 48, 60, 72, 96, and 120 h postdose. Cumulative urine specimens were collected over the intervals 0–6, 6–12, 12–24, 24–36, 36–48, 48–72, 72–96, and 96–120 h postdose.

### Potential Surrogate Marker of Activity

As a potential indicator of JD<sub>Tic</sub> effects on subject affect, the Profile of Mood States Standard instrument (POMS; Multi-Health Systems, North Tonawanda, NY) was administered (in the 'Right Now' recall period) on admission to the clinic and on Days 1–6 postdose.

## RESULTS

### Study Population

The first subject enrolled on 8 August 2011, and the final subject completed the trial on 12 December 2011. The demographic profile of the study population is summarized in Table 1. All subjects in the study were male. Six (50%) of the study subjects were of Hispanic ethnicity. The majority (9 of the 12 subjects) were white, 2 were black/African American, and 1 was Asian. Mean age was 31 years (range 19–44 years) and mean BMI was 25 kg/m<sup>2</sup> (range 22–28 kg/m<sup>2</sup>).

**Table 1** Summary of Subject Demographics

Subject demographics	Placebo (n = 6)	1 mg JD <sub>Tic</sub> (n = 6)	Overall (n = 12)
<i>Race, n (%)</i>			
Asian	0	1 (17%)	1 (8%)
Black or African American	0	2 (33%)	2 (17%)
White	6 (100%)	3 (50%)	9 (75%)
<i>Ethnicity, n (%)</i>			
Hispanic or Latino	4 (67%)	2 (33%)	6 (50%)
Not Hispanic or Latino	2 (33%)	4 (67%)	6 (50%)
Age in years, mean (SD)	27 (6)	35 (7)	31 (8)
Range	19–34	22–44	19–44
Height in cm, mean (SD)	167 (3)	174 (5)	170 (6)
Range	161–171	169–184	161–184
Weight in kg, mean (SD)	71 (8)	76 (9)	74 (9)
Range	62–83	61–89	61–89
BMI in kg/m <sup>2</sup> , mean (SD)	26 (2)	25 (2)	25 (2)
Range	23–28	22–27	22–28

Abbreviation: BMI, body mass index.

The demographic profiles of those subjects who received JD<sub>Tic</sub> 1 mg and those subjects who received placebo were similar, with the exception of race. All 6 subjects who received placebo were white vs 3 (50%) of the 6 subjects who received JD<sub>Tic</sub> 1 mg.

### Safety and Tolerability

There were no deaths and no SAEs reported during the study, and no AE led to an individual subject discontinuing the study prematurely.

Overall, there were 13 reported AEs: 9 AEs in the subjects who received JD<sub>Tic</sub> 1 mg and 4 AEs in the subjects who received placebo. Four unique subjects exposed to 1 mg JD<sub>Tic</sub> (67%) and 4 unique subjects who received placebo (67%) experienced at least one AE (Table 2). Six AEs were considered to be possibly related to the study medication, and four AEs were in three subjects who received JD<sub>Tic</sub>: VT (9 beats, 13.5 h postdose; Figure 1b), bradycardia and VT (7 beats, 11.5 h postdose; Figure 1c), and postural dizziness. The arrhythmias were asymptomatic and were detected the following mornings via review of the entire telemetry tracings by a cardiologist.

As specified in the JD<sub>Tic</sub>-001 protocol and DSMP, the two instances of NSVT in two subjects after administration of JD<sub>Tic</sub> (a 33% incidence in subjects receiving JD<sub>Tic</sub>) triggered a study termination rule. Both of these subjects subsequently underwent cardiac evaluations (21–41 days postdose), including echocardiograms, exercise myocardial perfusion studies, and treadmill stress tests. They remained asymptomatic, and no abnormalities were revealed. Protocol Amendment 3 (which allowed for the dosing of four additional subjects with placebo) was drafted to provide additional control subjects to better ascertain a relationship between the occurrence of NSVT and JD<sub>Tic</sub> administration. None of the four additional subjects dosed under Amendment 3 experienced NSVT during the study.

Other safety results were unremarkable: clinical chemistry, hematology, coagulation, urinalysis, orthostatic vital signs, 12-lead ECGs (including heart rate (Figure 2a), PR interval, QRS duration, and QTcB interval (Figure 2b)), and psychomotor functioning. As these figures show, the mean HR and QTcB duration were consistently slower and shorter for JD<sub>Tic</sub> than placebo subjects at all predose and postdose time points, although the differences were not statistically significant ( $p > 0.05$ ).

### Pharmacokinetics

JD<sub>Tic</sub> was not detected in the plasma of any subject (lower limit of quantitation 0.1 nM).

### Potential Surrogate Marker of Activity

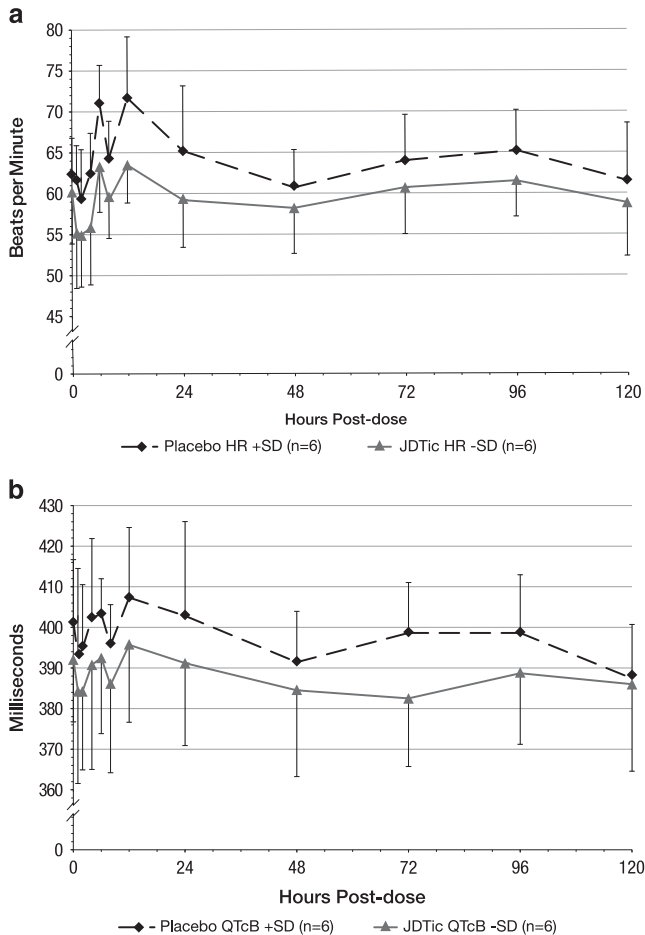
There were no significant differences in POMS scores between the placebo and JD<sub>Tic</sub> groups (Supplementary Table S1).

## DISCUSSION

In this first-in-human clinical trial of the KORAn JD<sub>Tic</sub>, six subjects received the starting oral dose of 1 mg and six

**Table 2** Adverse Events

Subject	Adverse event	Clinical principal investigator's assessment of causality	Treatment
I1102	Ventricular tachycardia (9 beats)	Possibly related	1 mg JD <i>Tic</i>
	Presyncope (unrelated to ventricular tachycardia)	Definitely not related	
I1103	Dizziness postural	Possibly related	Placebo
I2101	Bradycardia	Possibly related	1 mg JD <i>Tic</i>
	Ventricular tachycardia (7 beats)	Possibly related	
I2103	Somnolence	Possibly related	Placebo
I2104	Vessel puncture site pain	Definitely not related	1 mg JD <i>Tic</i>
	Vessel puncture site pain	Definitely not related	
	Dizziness postural	Possibly related	
	Dermatitis contact	Definitely not related	
I2105	Excoriation	Definitely not related	1 mg JD <i>Tic</i>
I3101	Dermatitis contact	Definitely not related	Placebo
I3103	Headache	Definitely not related	Placebo

**Figure 2** Subject electrocardiogram (ECG) heart rate and QTcB interval over time. (a) ECG heart rate. (b) QTcB interval.

subjects received placebo. JD*Tic* was undetectable in their plasma (LLOQ 0.1 nM). There were no deaths and no SAEs. Subjective AEs possibly related to study drug in placebo

subjects were postural dizziness (one instance) and somnolence (one instance). In JD*Tic* subjects, AEs comprised postural dizziness (one instance). There were no significant differences in clinical laboratory parameters (chemistry, hematology, coagulation, urinalysis), 12-lead ECG parameters, or WSF measures of psychomotor function. POMS scores did not differ between placebo and JD*Tic* subjects. However, two JD*Tic* subjects (33%) had asymptomatic single instances of NSVT on telemetry, triggering a study stopping rule.

We were surprised by the surfacing of a potential NSVT safety signal at the initial 1 mg dose. Applying the published 2–3.2% prevalence range of NSVT to the study population, the project statistician calculated the probability range of having exactly two otherwise healthy people with NSVT in a random sample of six people to be 0.006–0.013. In terms of study site experience with NSVT prevalence during the previous 9 years, it is estimated that approximately one in 3000 subjects showed an episode of NSVT. This is based on numerous studies which had cardiac rhythm monitoring either as a function of safety telemetry or as a function of thorough QT analysis. However, the full ECG/telemetry/Holter record was not reviewed by a cardiologist in all of these studies. Nevertheless, these site-specific data imply a very low prevalence.

Although the evidence is circumstantial, based on the temporal similarity of the 2 individual occurrences of NSVT out of 6 subjects (33%) who received JD*Tic*, the statistical unlikelihood that the 2 observed occurrences of NSVT were preexisting conditions in the affected subjects, the temporal similarity to the episode of NSVT observed in 1 of the 6 (17%) monitored monkeys dosed with JD*Tic*, and the existence of a possible causal mechanism, NSVT could be a JD*Tic* toxicity in humans. Certainly, there is no longer any commercial interest in the clinical development of JD*Tic*.

Given the preclinical and clinical data presented in the Introduction, it is plausible that JD*Tic* could have a direct cardiac interaction in human beings, although perhaps not through the classic KOR, which itself has myriad potential

cellular interactions (Bruchas and Chavkin, 2010). Although plasma JD<sub>Tic</sub> levels were unquantifiable (<0.1 nM) in this human study, there is preclinical data to suggest that 1 mg could be an efficacious human dose for KOR antagonism. The intragastric JD<sub>Tic</sub> AD<sub>50</sub> for inhibition of the effects of exogenous enadoline-induced behaviors (15 min postdose) in cynomolgus monkeys was 0.025 mg/kg, which would equate to an HED of 0.5 mg (with a predicted human C<sub>max</sub> of 0.02 nM) (data on file, RTI). Once again, these concentrations are much less than the lowest observed to cause prolongation of QTc in cynomolgus monkeys (>920 nM).

JD<sub>Tic</sub> activates JNK, which can in turn cause disruption of fatty acid oxidation in a human ventricular-derived cardiomyocyte cell line and cardiac dysfunction in mice, a potential mechanism through which JD<sub>Tic</sub> could cause cardiac dysfunction in humans. However, LY2456302 does not activate JNK (Melief *et al*, 2011); nevertheless, a single episode of NSVT was observed among 21 subjects (5%) who received at least one dose of LY2456302 in the first-in-human study (Lowe *et al*, 2014). The '5-beat ventricular tachycardia (occurred) approximately 8 h after a single 25-mg dose' in one of the eight subjects receiving that dose, but NSVT was not observed in any of the seven subjects receiving a 60-mg dose. The numbers are few, but here NSVT is not dose-related, so again the single episode might be unrelated to the KORAn activity of LY2456302. Still, given its occurrence and the NSVT that have been associated with naloxone, there remains the possibility that a human cardiac response to these agents could be associated more directly with the KOR itself and be a class effect of KORAn rather than specific toxicities associated with the molecules. It simply is impossible to know from the currently available data.

Given the therapeutic potential of the KORAn agents, it is imperative that further preclinical studies using human materials (eg, *in vitro* experiments with human cardiomyocytes) be conducted to clarify whether there is in fact a human cardiac effect of JD<sub>Tic</sub> or its metabolites; and, if so, the mechanism by which it occurs (ie, class effect or specific JD<sub>Tic</sub>-related toxicity). Depending on these *in vitro* data, further human trials of JD<sub>Tic</sub> might be considered.

## FUNDING AND DISCLOSURE

RTI International is a registered trademark and a trade name of Research Triangle Institute. RTI International holds the patent on JD<sub>Tic</sub>. This investigation was supported by the National Institute on Drug Abuse (NIDA) grant U19DA021002, for which Dr F Ivy Carroll served as Principal Investigator. JD<sub>Tic</sub> was designed and developed on Dr Carroll's NIDA R01 grant DA09045. Portions of this research were supported by NIDA contracts N01DA-0-8805, N01DA-4-8841, N01DA-8-8880, and the National Institutes of Health Bridging Interventional Development Gaps Program. Mr Jeffrey J Buda was a full-time employee of RTI Health Solutions at the time the study was conducted and in that capacity was also supported by this grant. Dr Thomas R Kosten is the Jay H Waggoner Chair and Professor of Psychiatry, Pharmacology, Neuroscience and Immunology and Pathology at the Baylor College of Medicine. Dr Dennis Swearingen is an employee of Celerion. Dr Bradford B Walters is a salaried employee of

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