Poster No. 12567

A next generation drug for overactive bladder, TRK-130, in a Phase-IIb clinical trial in Japan; Preclinical data of potent pharmacological effects based on modulation of neurotransmission.

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Hypothesis / aim of study

It is well-known that opioidergic modulation is involved in the control of the voiding pathway through spinal and supraspinal mechanisms(1); therefore, opioid receptor ligands have potential as drugs for overactive bladder (OAB). The aim of this study was to clarify the effect of TRK-130* on rhythmic bladder contraction and the voiding parameters in conscious or anesthetized animals in order to evaluate the therapeutic potential for OAB.

*A novel mu opioid receptor (MOR) partial agonist which has been subjected to a Phase IIb clinical trial in Japan.

Binding Affinities of TRK-130 to Human Mu-, Delta- and Kappa-Opioid Receptors

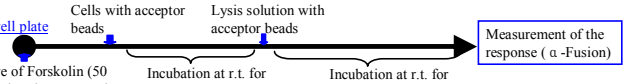
Test substance	Ki value (nmol/L)		
	mu-opioid receptor	delta-opioid receptor	kappa-opioid receptor
TRK-130	0.268±0.012	121±6	8.97±1.05
Morphine	11.5±0.4	1517±150	445±11

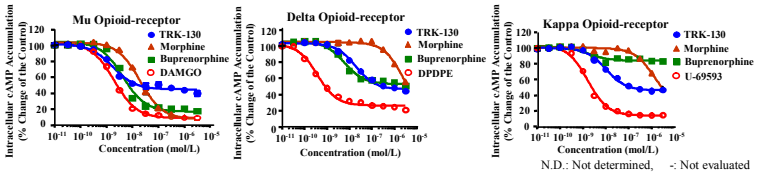
Cells stably expressed human mu-, delta- or kappa-opioid receptors were used for the assay.
Ki values represent the mean±SEM of those obtained from 3 experiments.

In binding assay, TRK-130 showed the higher selective affinity to the mu-opioid receptors.

Agonistic Activities of TRK-130 on Human Mu-, Delta- and Kappa-Opioid Receptors (Inhibition of Forskolin-induced Intracellular cAMP Accumulation)

Protocol cAMP determination: Alpha screening system (Perkinelmer)





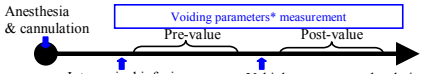
Test substance	Mu-opioid receptor		Delta-opioid receptor		Kappa-opioid receptor	
	EC50 (nmol/L)	Imax (%)	EC50 (nmol/L)	Imax (%)	EC50 (nmol/L)	Imax (%)
TRK-130	2.39 (1.85–3.09)	66.1±3.9 (a,b,c)	26.1 (22.4–30.5)	71.0±1.9 (d,e)	9.51 (8.40–10.8)	62.6±1.3 (d,e)
Morphine	19.9 (18.4–21.5)	100.0±1.0	N.D.	N.D.	N.D.	N.D.
Buprenorphine	4.49 (4.11–4.91)	90.8±1.4 (a,b)	8.00 (6.59–9.68)	62.2±2.4 (d)	2.08 (1.53–2.68)	20.5±0.7 (d)
DAMGO	2.07 (1.92–2.23)	100.0±0.9	–	–	–	–
DPDPE	–	–	0.527 (0.456–0.608)	100.0±0.7	–	–
U-69593	–	–	–	–	1.64 (1.55–1.73)	100.0±0.4

N.D.: Not determined, -: Not evaluated
Imax: Inhibition rate of the test substance against cAMP accumulation at the maximum concentration in comparison to the inhibition rate of the standard full agonist for each receptor subtype obtained at the maximum concentration (presented as mean±SEM of 6 wells obtained from 3 independent experiments).
EC50: 50% efficacy concentration relative to the inhibition rate of each test substance at the maximum concentration (the values in parentheses indicate the 95% confidence interval)
(a) $P<0.05$ vs. corresponding full agonist
(b) $P<0.05$ vs. morphine
(c) $P<0.05$ vs. buprenorphine
(d) $P<0.05$ vs. corresponding full agonist
(e) $P<0.05$ vs. buprenorphine

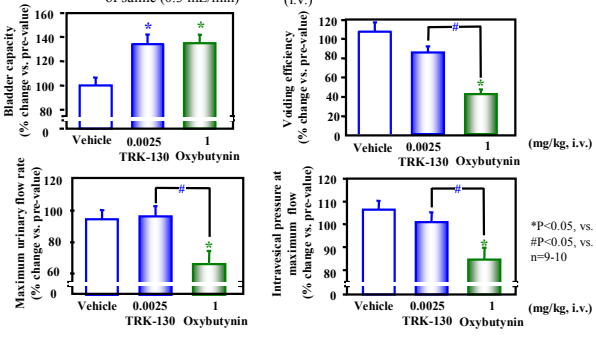
In cAMP assay, TRK-130 showed the higher selective affinity to the mu-opioid receptors and partial agonistic activity for all three of the human mu-, delta-, and kappa-opioid receptors, with the EC50 values of 2.39, 26.1, and 9.51 nmol/L, respectively.

Urodynamics Study in Anesthetized Guinea Pigs

Protocol 4- to 5-weeks-old male Hartley guinea pigs were used. TRK-130 or oxybutynin was first dissolved in 5% xylitol solution containing 0.02% or 0.1% citric acid



*: Bladder capacity (BC), Voiding efficiency (Ve), Maximum urinary flow rate (Qmax), Intravesical pressure at maximum flow (Pves (Qmax))



*P<0.05, vs. Vehicle-control
#P<0.05, vs. TRK-130-treated group
n=9-10

In the urodynamic evaluation, TRK-130 improved the ability to store urine without affecting voiding pressure or voiding efficiency unlike oxybutynin.

Other Pharmacological Profile of TRK-130

- Acetic acid writhing test : Effective (ED50, 0.0369 mg/kg, s.c.) in mice
- Neuropathic pain model : Effective (Seltzer, Chung, STZ-neuropathy model) in rodents
- Antinociceptive tolerance : No antinociceptive tolerance and cross-tolerance with morphine
- Gastrointestinal effect : No effect on GI transit in mice
- Psychological dependence : No reinforcing effect in self-administration test in rats and monkeys
- Physical dependence : Only slight withdrawal signs were seen in the repeated dosing test in rats (7 days treatment) and monkeys (28 days treatment)

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Effect of TRK-130 on Contraction of Rat-Isolated Urinary Bladder Induced by Electrical Field Stimulation

Protocol 5-weeks-old male SD rats were used in Magnus method. EFS condition; 10Hz, 1 ms duration for 5 sec, every 1 min.

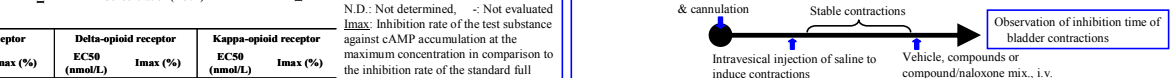
Test substance	Concentration (μmol/L)	Percentage of change from pre treatment value (%)
Vehicle[1)]	–	98.9±0.2
TRK-130	1	97.6±0.7
	10	93.7±1.6*

1): 10 % DMSO/ Distilled water with 0.1 w/v % of methanesulfonic acid
Values represent the mean±SEM of the results from 6 isolated urinary bladder samples.
*$P<0.05$ vs. corresponding vehicle control.

In the isolated bladder strips, TRK-130 demonstrated a limited direct effect on the bladder even at a high concentration of 10 μmol/L.

Rhythmic Bladder Contraction in Anesthetized Guinea Pigs

Protocol 5-weeks-old male Hartley guinea pigs were used. TRK-130 was first dissolved in 5% xylitol solution containing 0.02% or 0.1% citric acid



Test substance	Dose (mg/kg)	No. of guinea pigs	Inhibition time of bladder contractions (min.) Before	After	%MPE	ED30 (95% confidence interval) (mg/kg)
Vehicle	–	6	3.3±0.4	3.9±0.6	0.0±1.0	
TRK-130	0.00125	6	3.3±0.4	4.7±0.9	1.4±1.6	
	0.0025	6	3.2±0.5	18.0±8.5*	25.2±15.2	0.0034 (0.0014–0.0048)
	0.005	6	3.1±0.4	28.0±7.8*	43.0±13.9	
	0.01	6	3.3±0.2	45.9±5.5*	74.8±9.8	
Vehicle	–	11	3.3±0.2	3.5±0.3	0.0±0.5	
Morphine	0.25	10	3.3±0.2	5.5±0.7*	3.5±1.2	
	0.5	10	3.4±0.2	12.4±5.3*	15.7±9.5	0.62 (0.35–0.77)
	1	10	3.4±0.2	44.1±8.1*	71.9±14.3	
Vehicle	–	6	2.8±0.2	4.3±0.7	0.0±1.3	
Oxybutynin	1	6	2.8±0.5	5.0±1.5	1.2±2.7	–

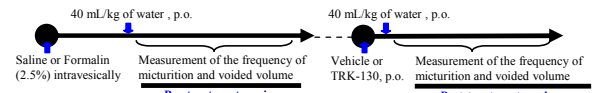
Treatment	No. of guinea pigs	Inhibition time of bladder contractions (min.) Before	After	%MPE	Ratio relative to the effect achieved by agonist alone (%)	AD50 (95% confidence interval) (mg/kg)
Vehicle	8	3.3±0.4	4.1±0.5	0.0±0.9	–	–
TRK-130 0.01 mg/kg alone	8	3.3±0.3	36.9±7.2*	58.8±12.9	100.0±22.0	
+ NLX 0.005 mg/kg	8	3.1±0.3	32.4±7.1	50.7±12.7	86.2±21.6	
+ NLX 0.01 mg/kg	8	3.3±0.2	24.7±7.9	36.9±14.0	62.9±23.9	0.012 (0.0056–0.027)
+ NLX 0.02 mg/kg	8	3.3±0.4	13.1±4.1	16.2±7.3	27.6±12.5	
+ NLX 0.04 mg/kg	8	3.0±0.4	3.9±1.1	-0.3±2.0	-0.5±3.4	
+ NLX 0.08 mg/kg	8	3.2±0.4	2.8±0.3	-2.3±0.5	-3.9±0.9	
Morphine 1 mg/kg alone	8	3.3±0.4	46.9±8.6*	76.6±15.3	100.0±20.0	
+ NLX 0.0005 mg/kg	8	3.2±0.3	42.1±8.8	68.1±15.8	88.8±20.6	0.0012 (0.00040–0.0031)
+ NLX 0.001 mg/kg	8	3.0±0.4	28.6±9.3	43.9±16.7	57.3±21.8	
+ NLX 0.002 mg/kg	8	3.2±0.3	13.8±6.6	17.4±11.9	22.7±15.5	
+ NLX 0.004 mg/kg	8	3.1±0.3	11.9±6.9	14.0±12.3	18.3±16.1	
+ NLX 0.008 mg/kg	8	3.2±0.3	5.8±0.7	3.1±1.2	4.1±1.6	

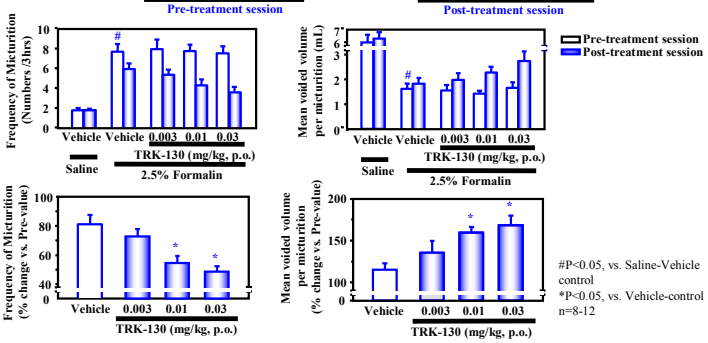
NLX: Naloxone
%MPE: Percentage of maximum possible effect, and it is calculated by the following formula,
[(Inhibition time in minutes in the drug-treated group - Inhibition time in minutes in the vehicle-treated group) / (60 - Inhibition time in minutes in the vehicle-treated group)] x 100
ED30: 30% Effective dose to increase the bladder capacity AD50: Dose to antagonize 50% of the response induced by TRK-130 or morphine alone
Values represent the mean±SEM. * $P≤0.025$ vs. corresponding vehicle control

TRK-130 and morphine both inhibited the development of micturition reflex, but the effect of TRK-130 was much stronger than that of morphine. The effects of TRK-130 and morphine were antagonized by naloxone, but their sensitivities to naloxone were significantly different (morphine has higher sensitive than TRK-130 to naloxone).

Voiding Behavior in the Urinary Frequency Model of Guinea Pigs

Protocol 6-weeks-old male Hartley guinea pigs were used. TRK-130 was first dissolved in 5% xylitol solution containing 0.02% or 0.1% citric acid





#P<0.05, vs. Saline-Vehicle control
*P<0.05, vs. Vehicle-control
n=8-12

In the cystitis model induced by intravesical application of formalin, oral administration of TRK-130 improved the urinary frequency and mean voided volume in guinea pigs.

Interpretation of Results

TRK-130 modulates voiding responses through the activation of MORs in the central nervous system and the decreases of sensory inputs from the bladder without affecting bladder contraction.

Concluding Message

1. TRK-130 is capable of ameliorating storage symptoms in patients with OAB.
2. TRK-130 is an exactly first in class drug candidate for OAB treatment, and has been undergoing a Ph-IIb in Japan as an partial MOR agonist, but is free from well-known common adverse effects (e.g. dependence) of MOR full agonists such as morphine.