Background

NKTR-181 is a new molecular entity opioid specifically designed to have a reduced rate and extent of abuse relative to its chemical analogs (1). NKTR-181 is a mu opioid agonist, with preclinical antinociceptive activity comparable to oxycodone and morphine, but with reduced abuse liability (2).

The chemical structure of NKTR-181 presents an improvement over analogs, independent of formulation.

NKTR-181 is currently in Phase 2 clinical studies in osteoarthritis patients with chronic pain of the knee.

Methods

NKTR-181 IV and PO pharmacokinetics were determined in male CD-1 mice (1 mg/kg; N=30) and 30 mg/kg/PO, 4 mice/timepoint), male Sprague-Dawley rats (1 mg/kg IV; 10, 20, 40, 60, 100, 300; and 550 mg/kg oral dose), and male Beagle dogs (1 mg/kg IV; 1, 1.5, 5, 15 mg/kg PO, 3 dogs, crossover design), in order to estimate interspecies population PK parameters. NKTR-181 solution (0.5%) or placebo (0.2% w/v) was administered via intravenous catheter. The limits of quantitation (LOQ) for NKTR-181 in plasma were 0.12 ng/mL in mice and 0.05 ng/mL in rat, dog, and human plasma. The in vivo protein binding of NKTR-181 in mouse, rat, dog, and human plasma was determined using equilibrium dialysis.

PK parameters were calculated using compartmental methods (WinNonlin Pro version 5.3). For interspecies allometric scaling, PK parameters obtained for each species with 2-compartmental analysis were plotted against corresponding body weights in log-log scale. Linear least-squares regression was applied to fit relationship to the equation:

\[ Y = aW^b \]

where \( Y \) = PK parameters, \( a \) = allometric coefficient, \( W \) = body weight, and \( b \) = allometric exponent.

The objectives of this work were:

- to characterize NKTR-181 pharmacokinetics in mice, rats, and dogs.
- to predict NKTR-181 exposure in the first in human (FIH) study, and then to compare predictions with results of the FIH study.

Results

Table: Mean (±SD) Plasma NKTR-181 Protein Binding in Mice, Rats, Dogs, and Humans (mmol/L)

<table>
<thead>
<tr>
<th>Species</th>
<th>0.03 µg/mL</th>
<th>0.3 µg/mL</th>
<th>3 µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>22 ± 9.0</td>
<td>11 ± 4.6</td>
<td>16 ± 1.0</td>
</tr>
<tr>
<td>Rat</td>
<td>23 ± 8.0</td>
<td>10 ± 4.0</td>
<td>20 ± 5.0</td>
</tr>
<tr>
<td>Dog</td>
<td>27 ± 15</td>
<td>8.5 ± 5.5</td>
<td>5.6 ± 3.3</td>
</tr>
</tbody>
</table>

In vitro plasma protein binding

NKTR-181 protein binding values for mice, rat, dog, and human plasma, determined using equilibrium dialysis, are presented in Table 1. Binding was low to moderate in all species, with the greatest extent of binding ranging from 33 to 45% in human plasma. There was a trend for binding to decrease in a proportional manner as concentration which appeared to be greater in rodent plasma than in dog and human plasma.

In vivo plasma protein binding

Mean plasma NKTR-181 concentration vs. time profiles for NKTR-181 concentrations in mice, rats, and dogs are shown in Figure 1. The concentration-time data were simultaneously fit with a two-compartment PK model parameterized in fixed effects. Interindividual population PK parameters were estimated also by mixed-effects modeling of plasma NKTR-181 concentration-time data from all animal species using Mixed-Effects Allometric Scaling. Predicted and observed plasma NKTR-181 unbound concentrations vs. time from the extent of drug absorption are presented in Table 2.

PO Pharmacokinetics

Mean dose-normalized plasma NKTR-181 concentration vs. time profiles after oral administration of 5 mg/kg NKTR-181 to mice, rats, and dogs, and 4 mg/kg in humans (320 mg fixed dose) are presented in Figure 2. AUC values were calculated using the trapezoidal rule, and dose-normalized AUC values were obtained over a wide dose range (10-500 mg) similar to that obtained in predose species.

Conclusions

- NKTR-181 exhibits dose-linear pharmacokinetics and good oral bioavailability in mice, rats, dogs, and humans.
- Results of the FIH study confirmed allometrically predicted CL/F and AUC.
- The pharmacokinetic characteristics of NKTR-181 support its progression into Phase 2 clinical trials.

References

1. Anesthesiology (2003;100;A303).