

# Preliminary Safety and Pharmacokinetic Results Following Administration of Ascending Single Doses of KNS-760704 to Healthy Volunteers

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## Introduction

### Background

KNS-760704 [(6R)-4,5,6,7-tetrahydro-N6-propyl-2,6-benzothiazole-diamine dihydrochloride monohydrate] is a putative neuroprotective agent in clinical development for the treatment of patients with amyotrophic lateral sclerosis (ALS). It is the (R)-(+)- optical enantiomer of the marketed compound pramipexole dihydrochloride (Mirapex<sup>®</sup>, (6S)-4,5,6,7-tetrahydro-N6-propyl-2,6-benzothiazole-diamine, Boehringer Ingelheim), a potent dopamine agonist with selective high affinity for the D<sub>2</sub> and D<sub>3</sub> sub-types. Both the (R)-(+)- and (S)-(-)- enantiomers have been shown to possess neuroprotective properties. In contrast to Mirapex<sup>®</sup>, however, KNS-760704 has very low affinities for D<sub>2</sub> and D<sub>3</sub> dopamine receptors and should be better tolerated at higher doses. The hypothesis for this clinical development program is that KNS-760704, if dosed at much higher levels than Mirapex<sup>®</sup>, will be an effective treatment for ALS.

### Objectives

The objectives of this single-site, randomized, double-blind, placebo-controlled study were to determine the safety, tolerability, and pharmacokinetics of ascending single doses of KNS-760704 in healthy volunteers, and to determine the preliminary effect of food on absorption of KNS-760704.

## Methods

This was a single-center, randomized, double-blind, placebo-controlled, ascending single-dose study to determine the safety and tolerability of KNS-760704 when administered orally to adult female and male volunteers. Single dose pharmacokinetics and the effect of food on drug absorption and elimination were assessed as secondary objectives. Safety observations included vital signs, physical

examination, clinical laboratory tests, ECGs, and adverse event reporting. Blood and urine samples were collected pre-dose and for 72 hours post-dose to assess the pharmacokinetics.

A total of 30 subjects were enrolled in the study and took study drug or placebo; 18 subjects (60%) were male and 12 (40%) were female. Ages ranged from 30 to 58 years, with a mean age of 44.2 years. Six subjects received capsules containing either placebo, 50 mg KNS-760704 (fasted), 150 mg KNS-760704 (fasted), 300 mg KNS-760704 (fasted), or 150 mg KNS-760704 (fed). The 4 dose panels were enrolled sequentially and all available safety data were reviewed under blinded conditions for serious safety or tolerability events before proceeding to the next dose level. All subjects completed the study as planned.

## Results

No deaths, serious adverse events, or adverse events that led to premature discontinuation occurred during the conduct of the study. One or more adverse events were reported by 50% of the study participants and the intensity of adverse events was generally mild. Adverse events were reported by 67% of subjects in the placebo group, by 33% of subjects in the 50 mg group, and by 50% each of subjects in the 150 mg, 300 mg, and Fed 150 mg groups. The most frequent adverse event was dizziness, reported by 6 of 30 (20%) total study subjects, by 3 of 6 (50%) subjects in the placebo group and by 1 of 6 (17%) subjects in each of the 150 mg, 300 mg, and fed 150 mg groups. The adverse event profile in each active dose group was similar to that in the placebo group and there was no evidence suggesting that any specific treatment-emergent adverse events occurred with greater frequency in subjects receiving KNS-760704 than in subjects receiving placebo. There was no evidence of clinically significant effects of

KNS-760704 on heart rate or blood pressure and specifically no evidence of orthostatic hypotension. There were no clinically significant or dose-dependent changes from baseline on physical exams or ECGs. There were no clinically significant laboratory abnormalities judged to be drug related. Pharmacokinetic data indicated that KNS-760704 is rapidly absorbed with mean maximum concentrations (C<sub>max</sub>) of 125, 360, 781, and 315 ng/mL reached at approximately 2 to 2.5 hours post-dose for the 50, 150, 300 and 150 (fed) mg dose groups, respectively (**Figure 1** and **Table 1**). Mean exposures (AUC<sub>0-∞</sub>) were 1254, 3815, 8623, and 3397 h\*ng/mL for the 50, 150, 300 and 150 mg (fed) dose groups, respectively. Both C<sub>max</sub> and AUC increased in proportion to dose across the dose levels tested. The mean T<sub>1/2</sub> was independent of dose. Comparison of the mean plasma concentrations and mean pharmacokinetic parameters after administration of a single 150 mg dose following a high fat/high calorie breakfast with those after administration of a 150 mg dose under fasted conditions demonstrates essentially no effect of a meal on the absorption and elimination of KNS-760704. Urinary recovery of unchanged KNS-760704 was comparable across the two fasted cohorts for which complete urine collections were available and the food-effect panel, averaging 94.7% for the 50 mg fasted cohort, 88.3% for the 300 mg fasted cohort, and 88.6 % for the 150 mg fed cohort (**Figure 2**). Excretion appears to be essentially complete by 36 hours after drug administration, consistent with the ~7-hour T<sub>1/2</sub>.

## Conclusions

Preliminary results of this study demonstrate that single oral doses of 50, 150, and 300 mg KNS-760704 are safe and well-tolerated. The drug is orally bioavailable and the pharmacokinetics are linear. Absorption and elimination are not affected by a high fat/high calorie meal.

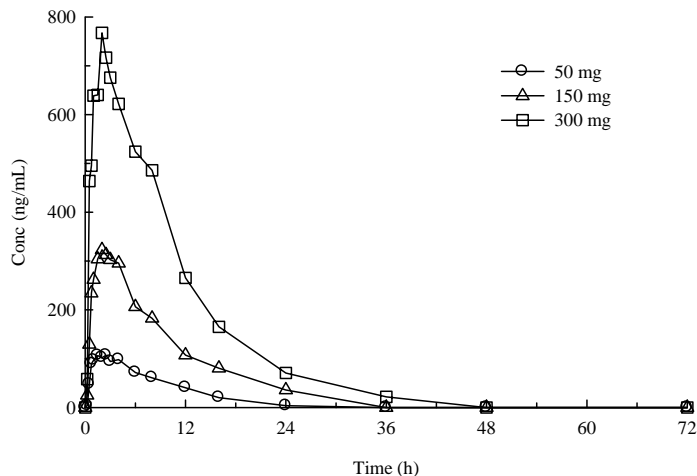
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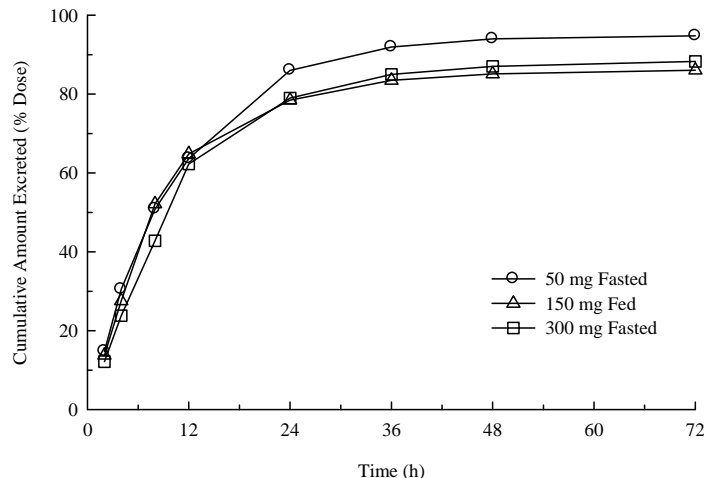
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**Figure 1.** Mean plasma KNS-760704 concentrations after oral administration of single 50 mg, 150 mg, and 300 mg doses to adult volunteers under fasted conditions — linear axes.



**Figure 2.** Mean cumulative urinary excretion of KNS-760704 after oral administration of single 50 mg (fasted), 150 mg (fed), and 300 mg (fasted) doses to adult volunteers — percent of dose.



**Table 1.** Summary of pharmacokinetic parameters for KNS-760704 after oral administration of single 50 mg, 150 mg, and 300 mg doses to adult volunteers under fasted conditions and 150 mg under fed conditions

Parameter <sup>1</sup>	Fasted			Fed
	50 mg	150 mg	300 mg	150 mg
C <sub>max</sub> (ng/mL)	125 ± 22.0 (6)	360 ± 60.4 (6)	781 ± 158 (6)	315 ± 062 (6)
T <sub>max</sub> (h)	2.04 (6)	2.04 (6)	1.98 (6)	2.58 (6)
AUC(0-t) (h•ng/mL)	989 ± 295 (6)	3,360 ± 780 (6)	8,340 ± 3,203 (6)	3,080 ± 934 (6)
AUC(inf) (h•ng/mL)	1,254 ± 347 (6)	3,782 ± 1012 (5)	8,624 ± 3,263 (6)	3,379 ± 957 (6)
λ <sub>z</sub> (h <sup>-1</sup> )	0.1064 ± 0.0171 (6)	0.1001 ± 0.0087 (5)	0.1151 ± 0.0309 (6)	0.1144 ± 0.0259 (6)
t <sub>1/2</sub> (h)	6.65 ± 1.07 (6)	6.96 ± 0.56 (5)	6.40 ± 1.73 (6)	6.33 ± 1.49 (6)
CL/F (mL/min)	527 ± 135 (6)	524 ± 146 (5)	492 ± 194 (6)	581 ± 127 (6)
V <sub>z</sub> /F (L)	294 ± 46.2 (6)	311 ± 068 (5)	258 ± 73.5 (6)	308 ± 55.9 (6)
U <sub>e</sub> (mg)	35.3 ± 5.19 (6)	74.8 ± 50.17 (6)	198 ± 28.0 (6)	96.9 ± 4.71 (6)
Fe (% Dose)	94.7 ± 13.9 (6)	66.9 ± 44.8 (6)	88.3 ± 12.5 (6)	86.6 ± 4.21 (6)
CL <sub>r</sub> (mL/min)	628 ± 149 (6)	385 ± 236.5 (6)	441 ± 159 (6)	559 ± 140 (6)

<sup>1</sup>Mean ± standard deviation (N) except for T<sub>max</sub> for which the median (N) is reported.