T2346

Pharmacokinetics (PK) and Pharmacodynamics (PD) of YKP10461 Following a First-in-Human Phase I Study in Healthy Participants

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BACKGROUND

- YKP10461 is a new chemical entity currently under investigation for the treatment of neurological diseases. It is a novel small molecule, a non-propargyl amine that functions as a reversible and highly selective monoamine oxidase B (MAO-B) inhibitor. YKP10461 is a hydrophobic compound that is practically insoluble in water. In order to facilitate gastric absorption, a hot melt extruded drug product formulation was developed.
- MAO-B has been identified in human brain tissue, and its activity increases with age (Ref 1). Inhibition of this enzyme is one of the important therapeutic strategies for the treatment of Parkinson's Disease (PD) (Ref 2). YKP10461 is being developed as a potential drug for the treatment of PD based on its biochemical action *in vitro* and its reduction of motor complication properties *in vivo* along with a favorable safety profile. In addition, preclinical studies suggest that YKP10461 may slow the progression of the disease as well as provide palliative relief of the symptoms of PD, notably dyskinesia, a limitation of current medications (Ref 3).
- Pharmacokinetic (PK) results are reported from the First-in-Human (FIH) single ascending dose (SAD) study. Additional analyses of the plasma evaluated the activity of MAO-B and inhibition of MAO-B and MAO-A in the same population.

OBJECTIVES

- To evaluate PK of single ascending oral doses of YKP10461 in healthy male and female participants.
- To measure three biomarkers in a sequential decision tree structure with each part leading to a data-driven decision to proceed with further analyses.

METHODS

Study Design

- A double-blind, randomized, placebo-controlled, human SAD study.
- 60 healthy participants were enrolled at a single center: 10 participants (7 active and 3 placebo) in each of 6 sequential cohorts. The following oral doses of YKP10461 were administered (fasting conditions): 10, 25 (2.5-fold increase), 50 (2-fold increase), 100 (2-fold increase), 200 (2-fold increase), and 250 mg (1.25-fold increase).

Pharmacokinetics

- 42 participants received active YKP10461 and were included in the PK analyses.
- Blood samples for the determination of plasma YKP10461 concentration were collected predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 16, 24, 36, and 48 hours postdose (assayed by a validated GLP LC-MS/MS method).
- The following PK parameters were presented for plasma YKP10461:
  - AUC_{0-t} : Area under the plasma concentration versus time curve from time 0 to the time of the last measurable concentration
  - AUC_{0-inf}: Area under the plasma concentration versus time curve from time 0 to infinity
  - C_{max} : Maximum measured plasma concentration
  - t_{max} : Time at which C_{max} occurred
  - $t_{½}$: Apparent terminal elimination half-life
  - CL_{po} : Apparent total body clearance after extravascular administration
  - Vd/F : Apparent volume of distribution after extravascular administration
- The following statistical methods were employed:
  - PK parameters were summarized by dose group using descriptive statistics.
  - Dose proportionality was evaluated using a regression approach.

Pharmacodynamics

- All 60 participants were included in the PD analyses.
- Blood samples for *in vitro* assessment of YKP10461 inhibitory effect on MAO-B enzyme activity were collected predose and at 2, 4, 6, 12, 24, 36, and 48 hours postdose and assayed at the University of Zurich.
- Blood samples for analyses of the plasma levels of phenylethylamine (PEA) (MAO-B enzyme substrate) and 3, 4-dihydroxyphenylglycol (DHPG) (MAO-A enzyme inhibition index) were collected predose and at 12, 24, 36, and 48 hours postdose.

Analysis Methods

Analyte	Method	Internal Standard	MRM	Analytical Range
YKP10461	MS/MS	13C6-YKP10461	325.3-264.2	0.5-500 ng/mL
MAO-B	Western Blot(2)	Resurfin	N/A	0.016-1.0 mg/mL
PEA	MS/MS	Phenyl-3-Propylamine	122.3-105.2	0.25-100 ng/mL
DHPG	MS/MS	D5-DHPG	169.3-151.2	0.20-20 ng/mL

RESULTS

Table 1: Plasma YKP10461 Pharmacokinetic Parameters Following Single Oral Dose Administration of 10 to 250 mg YKP10461 to Healthy Participants

YKP10461 Dose (N)	Cmax (ng/mL)	AUC 0-inf (ng*hr/mL)	AUC 0-t (ng*hr/mL)	Tmax (hr)	T1/2 (hr)	CLpo (L/hr)	Vd/F (L)
10 mg (N = 7)	16.1 (66.3%)	199 (36.4%)	165 (41.3%)	4.00 (2.51-6.04)	22.1 (3.73)	52.8 (16.4)	1711 (663)
25 mg (N = 7)	71.3 (34.3%)	747 (38.1%)	687 (37.5%)	3.00 (2.51-4.00)	14.9 (3.52)	35.3 (11.8)	750 (269)
50 mg (N = 7)	134 (30.9%)	1432 (28.9%)	1370 (28.8%)	4.00 (1.50-4.24)	10.9 (2.89)	36.1 (9.55)	570 (237)
100 mg (N = 7)	248 (28.3%)	3177 (32.7%)	2862 (30.0%)	3.00 (2.00-4.00)	15.2 (3.19)	32.9 (10.3)	700 (165)
200 mg (N = 7)	611 (35.9%)	7732 (39.8%)	6875 (41.9%)	3.00 (2.00-6.00)	15.9 (3.96)	27.9 (14.3)	643 (371)
250 mg (N = 7)	808 (30.7%)	8927 (21.4%)	8410 (22.7%)	3.00 (2.50-6.00)	12.3 (2.65)	28.6 (6.24)	512 (180)

Note: Cmax and AUC are presented as geometric mean (CV%);
Tmax is presented as median (range);
T1/2, CLpo, and Vd/F are presented as arithmetic mean (SD)

Figure 1: Pharmacokinetics of YKP10461 in Humans: Currently in Phase I Studies

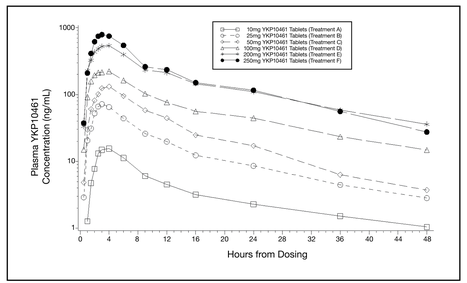


Figure 2: MAO-B Levels are Inhibited and PEA Levels Increased in Participants Dosed with YKP10461

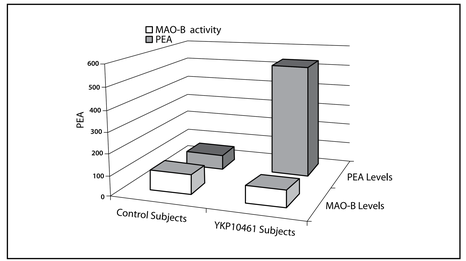
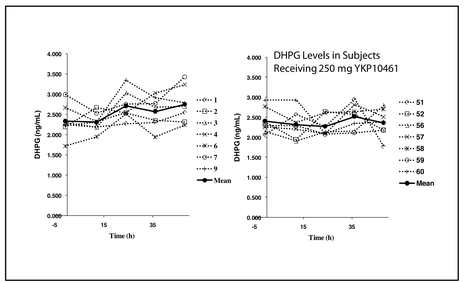


Figure 3: DHPG Levels: No Significant MAO-B Involvement in Dosed Participants, Compared to Placebo



Pharmacokinetic Results:

- Concentration-time profiles of YKP10461 in plasma were well characterized following single oral administrations of 10 to 250 mg doses to healthy participants following an overnight fast.
- Peak YKP10461 plasma concentrations were generally observed between 3 and 4 hours postdose and the concentrations remained measurable for 48 hours postdose. Mean apparent terminal elimination half-life typically ranged from 11 to 16 hours.
- Plasma YKP10461 exposure (AUC, Cmax) increases were dose dependent and they were approximately dose proportional for the 25 to 250 mg dose range.

Pharmacodynamic Results:

- Three biomarkers, phenylethylamine (PEA), monoamine oxidase B (MAO-B) and dihydroxyphenyl glycol (DHPG) were analyzed in plasma and blood.
- There was an elevation of PEA at all YKP10461 dose levels, compared to placebo participants and every dose group receiving YKP10461 also exhibited MAO-B inhibition compared to the placebo. There was a statistically significant correlation of PEA levels and MAO-B inhibition. These results imply that YKP10461 may have efficacy at levels lower than 10 mg/participant.
- There was no statistical change in DHPG concentrations between the YKP10461 and placebo groups at the lowest (10 mg/participant) and the highest dose (250 mg/participant). These results show no inhibition of MAO-A which in turn suggests that this drug would not be expected to present a risk of a tyramine-mediated increase in blood pressure.

CONCLUSIONS

Exposure-related PD effects at all dose levels studied support proof of mechanism for MAO-B inhibition by YKP10461. Inhibition of MAO-B was demonstrated at all doses, from lowest to highest. No MAO-A enzyme inhibition was evident at the lowest and the highest doses. These PK and PD results support the achievement of clinically relevant YKP10461 exposures, applicable to future clinical studies of YKP10461, and suggest that YKP10461 may be effective in the treatment of Parkinson's Disease.

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