BACKGROUND

- YKP10461 is a new chemical entity currently under investigation for the treatment of neurodegenerative diseases. It is a non-proprietary aminopyridine that functions as a reversible and highly selective monamine oxidase B (MAO-B) inhibitor. YKP10461 is a hydrophilic 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). YKP10461 has been developed as a potential drug for the treatment of PD based on its biochemical action in vivo and its reduction of motor complication properties in vivo along with a favorable safety profile. In addition, preclinical data suggest that YKP10461 may slow the progression of the disease as well as provide palliative relief of the symptoms (Ref 2, notably dyskinesia, a limitation of current medications (Ref 3)).

OBJECTIVES

- To evaluate PK of a single ascending oral doses of YKP10461 in healthy male and female participants.
- To measure three biomarkers in a sequential decision tree structure following oral administration of YKP10461 to healthy Participants.

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.

Participants

- All 60 participants received active YKP10461 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, 3, 4, 6, 12, 16, 24, 36, and 48 hours postdose (as advised by a validated GPC LC-MS/MS method).
- The following PK parameters were presented for plasma YKP10461:
  - Cmax: Area under the plasma concentration versus time curve from time 0 to the time of the last measurable concentration
  - Tmax: Time at which Cmax occurred

Pharmacokinetics

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<th>Dose (mg)</th>
<th>N</th>
<th>Tmax (hr)</th>
<th>Cmax (ng/mL)</th>
<th>CLpo (L/hr)</th>
<th>Vd/F (L)</th>
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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 generally occurred between 3 and 4 hours postdose, and concentrations remained measurable for 48 hours postdose. Mean apparent terminal elimination half-life typically ranged from 11 to 15 hours.

Pharmacodynamic Results:

- These biomarkers, phenethylamine (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 as well. Also, there was a statistically significant correlation of PEA levels and MAO-B inhibition. These results imply that YKP10461 may have efficacy at lower than 10 mg dose levels.
- There was no statistical change in DHPG concentrations between the YKP10461 and placebo groups at the lowest (10 mg) dose and the highest dose (250 mg) dose.

Pharmacodynamic parameters:

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

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CONCLUSIONS

- Exposure-related PD effects at all dose levels used in this study were not indicative of a potential for PD-related risk.
- No inhibition of MAO-A was observed in this study.

REFERENCES

1. Mostafaie, N, Jungwirth, S, Huber, K, Tragl, KH, Danielczyk, W and Riederer, P. Oxidative stress and dihydroxyphenyl glycol (DHPG) were analyzed in plasma and blood.

2. There was no statistical change in DHPG concentrations between the YKP10461 and placebo groups at the lowest (10 mg) dose and the highest dose (250 mg) dose.

3. These biomarkers, phenethylamine (PEA), monoamine oxidase B (MAO-B) and dihydroxyphenyl glycol (DHPG) were analyzed in plasma and blood.

4. There was a statistically significant correlation of PEA levels and MAO-B inhibition. These results imply that YKP10461 may have efficacy at lower than 10 mg dose levels.

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