Novel Monthly Long-Acting Injectable Rasagiline Prodrug

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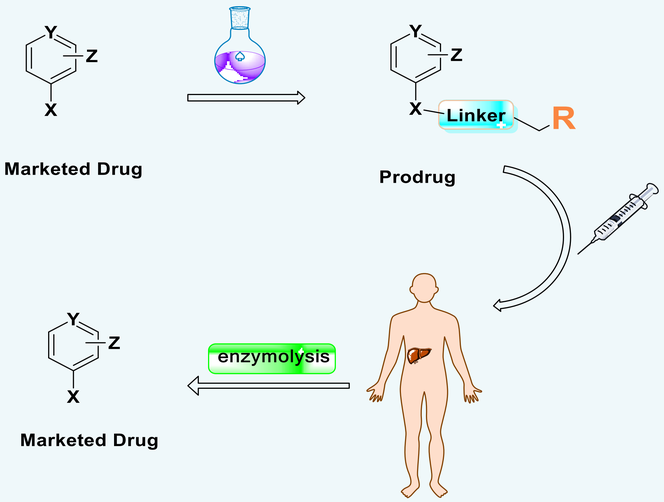
Mechanism of Prodrug Based Long-Acting Injectable (LAI)

LAI Prodrugs are designed to obtain compounds with low solubility, high melting point, and stable crystalline form. After IM or SC administration, the drug forms a depot in vivo, slowly releases in blood stream then rapidly transformed to the parent drug.
The marketed drug paliperidone palmitate (once every 6 months) and aripiprazole lauroxil (once every 2 months) and others have validated LAI based prodrug technology.



HNC364: Rasagiline Prodrug Based LAI for PD

HNC364

- Rasagiline prodrug suspension injection, once every 1–2 months administration by IM.
- Slowly release but rapidly transform to active compound Rasagiline after IM injection.
- NME patent granted in the US, EU and Japan.
- Stable for 24 months at condition (25 ℃ / 60% RH).

Targeted Market

- PD currently affects 13 million people worldwide and is estimated to affect 32 million by 2050.
- Global PD Therapeutics Market estimated to reach $10.5 Billion by 2029.
- Only 10-20% of PD patients are fully adherent to long-term treatment, a huge unmet need for lifecycle medication management by LAIs.

Strength

- HNC364 is the only MAO-B LAI with an ultra-long- acting profile with a once-every 1-2 months regimen for optimal long-term medication.
- Prodrug of Rasagiline injection has a high technological barrier, is the only patented ultra long-acting formulation in PD treatment.

Regulatory Progress

- Phase I SAD study in the US completed and no SAE observed.
- SAD and Pop PK/PD results well support once 1-2 months IM injection administration with 40mg-80mg dose regimen.
- Positive feedback from FDA to support the clinical pathway to conduct a PK bridging study then move into Phase 3 which is expected in 2025.

HNC 364 Preclinical Safety Summary

Safety pharmacology

- hERG test: IC50 >3.432 μM
- Beagle dogs (cardiovascular system): no obvious effects
- SD rats (respiratory system and central nervous system) : no obvious effects

Single-dose toxicity

- SD rats: Maximum tolerance dose (MTD) ≥ 100 mg/kg
- Beagle dogs: Maximum tolerance dose (MTD) ≥ 50 mg/kg

Repeat-dose toxicity

- SD rat: NOAEL is 20 mg/kg
- Beagle dogs: NOAEL is 10 mg/kg

Genotoxicity

- Ames test: Negative
- Chromosome Aberration Assay in CHL Fibroblast: Negative
- Micronucleus Assay in SD Rat: Negative

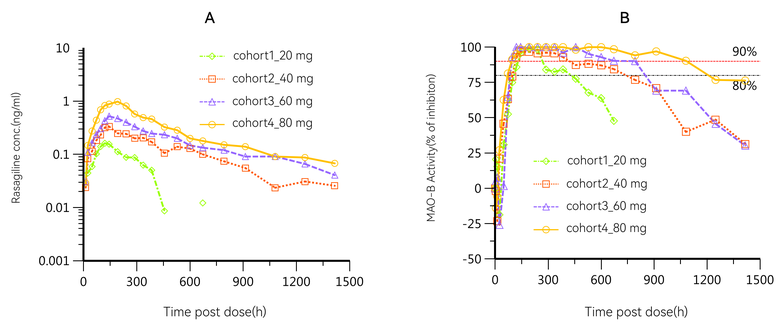
Other Tox studies

- Active sensitivity test: Negative
- Hemolysis test: Negative
- Local irritation study: intramuscular granulomatous inflammation at application site were observed in 3 and 10 mg/kg groups, no obvious recovery was noted only in the 10 mg/kg group after 8-week recovery phase.

HNC364 Phase I PK/PD Result

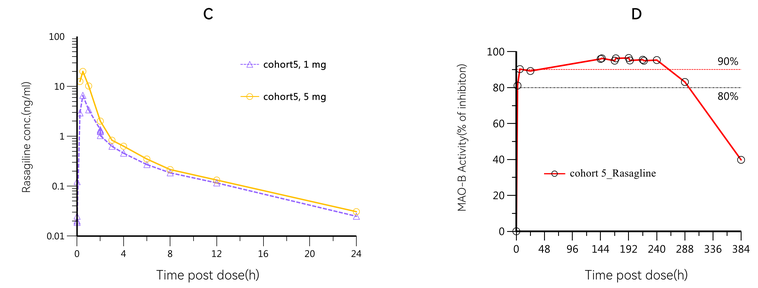
Pharmacokinetic (PK) and pharmacodynamic (PD) studies were conducted following single ascending doses (SAD) of HNC364 in healthy volunteers. Platelet MAO-B activity was utilized as a PD biomarker*. Additionally, a cohort of subjects received multiple oral doses of the marketed drug rasagiline (AZILECT®) as a positive control (Figure 1).
*Research indicates that inhibiting MAO-B activity by over 80% in the central nervous system influences central dopamine levels[1]. Furthermore, a strong positive correlation exists between MAO-B inhibition rates in the brain and platelets following the administration of an MAO-B inhibitor[2].

Figure 1. Plasma Concentration of Rasagiline and MAO-B Activity Inhibition Following HNC364 or Rasagiline Administration.



(A) Plasma concentration-time profiles of rasagiline after a single dose of HNC364 (20 mg, 40 mg, 60 mg, or 80 mg; Cohorts 1-4)

(B) Percentage inhibition of MAO-B activity in Cohorts 1-4 following a single dose of HNC364

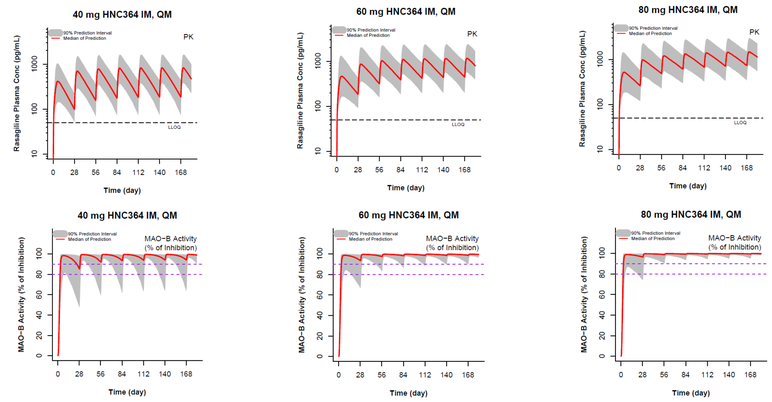


(C) Plasma concentration-time profile of rasagiline in Cohort 5 after multiple oral doses of rasagiline (5 mg on Day 1, followed by 1 mg daily until Day 10)

(D) Inhibition of MAO-B activity in Cohort 5 following multiple oral doses of rasagiline.

Using the population PK/PD model, various HNC364 doses administered via intramuscular injection once every month were simulated (Figure 2).

Figure 2. Predicted Rasagiline Exposure and MAO-B Inhibition Following Multiple Intramuscular HNC364 Doses.



This figure illustrates the predicted systemic exposure of rasagiline and its inhibitory effect on MAO-B activity following repeated intramuscular administrations of HNC364 every 4 weeks. Simulations were conducted in 1,000 virtual subjects using the final PK/PD model for each dose level. The solid lines represent the median predicted values for rasagiline plasma concentration and MAO-B inhibition from baseline, while the dashed lines show the 90% prediction intervals (5th and 95th percentiles), reflecting the range of inter-individual variability in response.

Key Findings

- The prodrug HNC364 was not detected in plasma.
- Single doses of 60 or 80 mg of HNC364 achieved >90% inhibition of MAO-B activity at 4 weeks post-dose.
- Simulation results from the population PK/PD model indicate that repeated 60 mg doses of HNC364, administered intramuscularly every 4 weeks, maintained MAO-B activity inhibition above 90%.
- No SAE observed

This study result supports that HNC364, a prodrug of rasagiline, can provide sustained MAO- B inhibition with monthly dosing and is well tolerated.

[1] Regensburger M, Ip CW, Kohl Z, Schrader C, Urban PP, Kassubek J, Jost WH (2023) Clinical benefit of MAO-B and COMT inhibition in Parkinson's disease: practical considerations. Journal of Neural Transmission 130, 847-861.

[2] Kettler R, Cesura AM, Dingemanse J, Prada M (1990) MAO-B inhibition in rabbit tissues and in human platelets by Ro 19-6327 shows similar time-course. In Amine Oxidases and Their Impact on Neurobiology, Springer Vienna, pp. 211-214. http://dx.doi.org/10.1007/978-3-7091-9113-2_31.

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