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"Medicine, reinvented"

LYNX is a customizable, modular drug delivery platform for QW LAO therapies.

Technology overview.

- Capsule is swallowed and enters the stomach (a proprietary coating makes the capsule easy to swallow).
- The capsule dissolves once in the aqueous environment of the stomach and the drug arms emerge.
  - The design and engineering of the LYNX technology keeps it in the stomach and makes it impervious to the normal conditions of eating and drinking.
  - Linkers allow the drug arms to flex and bend so food can pass.
- Drug arms consistently release API for 7 days.
  - Specific polymers are designed to break down in a timed fashion.
- When the dosing period is complete, the linkers soften and disintegrate (the LYNX technology loses its conformational shape)
  - The remnants are passed as undigested fiber.

Platform customizability.

- Drug arms can be formulated with a range of APIs, API combinations, and different dosage strengths.
- Drug release duration – modifying one linker changes the timing of polymer breakdown and modulates when the technology exits the body.

Our development approach is value-driven and quickly advances LAO products.

- We leverage existing evidence and modeling/simulation.
  - Builds a strong scientific rationale.
  - Accelerates programs from *in vitro* to clinical and regulatory pathways.
- Innovation development is focused on the end goal and the patient.
  - Achieve a drug release profile that improves PK/PD and drives pharmaco-economic outcomes.
  - Aligned with patient acceptance attributes.

Accelerated development of QW LAO risperidone for schizophrenia (LYN-005).

Modeling and simulation work enabled quick advancement to the first oral administration.

- PK modeling for preliminary LYN-005 dose selection.
  - ***Guided by existing data from immediate-release (IR) and LAI risperidone formulations already in use.***
  - Simulated PK profiles for QW LYN-005 (14, 15, and 16mg); examined overlap patterns and time to reach steady state concentrations.
- Clinical outcome modeling to understand the drivers of efficacy for a tailored therapeutic profile.
  - ***Leveraged published data and learnings from simulated LYN-005 concentrations***.
  - Simulated Positive and Negative Symptom Scale (PANSS) score profiles for selected LYN-005 and IR doses and steady-state exposure metrics.
    *PANSS score-time profiles were similar for LYN-005 (15, 30, 45mg) and IR (2, 4, 6mg), but LYN-005 had less variation.
    *Css,min is likely the most sensitive and predictive of PANSS score (no trend noted for Css,ave vs PANSS score; PANSS score decreased slightly as Css,min increased).
    *LYN-005 (15, 30, 45mg) expected to produce Css,min values > 5.2ng/mL (effective concentration, Reddy et al).

Aligning the first clinical study design with FDA endpoints enabled approval to bridge to established efficacy and accelerated the clinical/regulatory pathway.

- P3 pivotal PK comparability study (n=90, 45 per dosage strength).
  - Patients stable on any oral anti-psychotic switched to IR oral risperidone (2mg or 6mg) x 7 days (oral run-in), then inpatient LYN-005 dosing for 5 weeks (QW LYN-005 + IR [15mg/1mg or 45mg/3mg] x 7days, then QW LYN-005 [15 or 45 mg] x 4 weeks).
  - PK assessed weekly through week 5 (endpoint); each participant served as their own control.

- ***Pre-agreed FDA endpoints using a PK-bracketing approach to demonstrate efficacy*** (90% confidence interval).
  1. C_{min} target (one-sided LYN/IR >0.80): Lower bound of efficacy (C_{min} drives efficacy; maintain drug concentrations above QD IR).
  2. C_{max} target (one-sided LYN/IR <1.25): Upper bound of safety (Efficacy caps at 60% occupancy of dopamine receptors; higher concentrations increase side effects, not efficacy).
  3. C_{ave} target (two-sided LYN/IR 0.80-1.40): Confirm efficacy (C_{ave} not needed, but agreed to; the interval is based on a clinical and scientific PK argument).

- ***FDA endpoints were met at the planned interim analysis (n=46), enabling early trial cessation*** (SIRS 2024).
  - Preliminary dose-normalized mean PK profile of the active moiety (n=9).
    Oral run-in**:** drug concentrations > 10ng/mL (target for dose normalization), but with high peak-to-trough variation.
    Week 5 of LYN-005: ***drug concentrations remained within a narrow therapeutic window for 7 days (up to next dose).***
  - Parallels noted between LAO formulation and LAI antivirals may translate to better patient outcomes.
    Cmax is typically blunted by 30%, and Cmin is elevated slightly.

LYNX technology is being used to advance other drugs as LAO therapies.

Formulation experience.

- A wide range of APIs with different potency, solubility, and molecular weight (MW) can be embedded in the drug arms.
- High solubility APIs are straightforward to formulate and achieve near zero-order drug release over one week.
- Co-administration of APIs is possible.

Important parameters for embedded formulations.

- Dose level, 0.1N HCl solubility, MW, half-life, and melting temperature (T_m).
- T_m is particularly important; HME (120° C) is used to mix the drugs and polymers in the drug arms.

Summary.

- We developed the first QW oral administration product that is based on continuous drug release over a 7-day period.
- We are tuning the product technology and using our *in vitro* methodology to rapidly advance different drugs and achieve longer dosing intervals.
  - Determine and model the release rate required to predict a clinical outcome in humans.
    API with a long half-life – preclinical studies in dogs show that the LAO formulation maintains desired plasma drug concentrations (avoid Cmax and Cmin) up to 336 hours (14 days).
  - Extend the technology residence time – one linker changes the time to technology break down and exit.
    Most recent dog data demonstrate residence of the technology up to 21 days.