Inhibition of SLC6A19 as a Therapeutic Approach for the Treatment of PKU

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Introduction

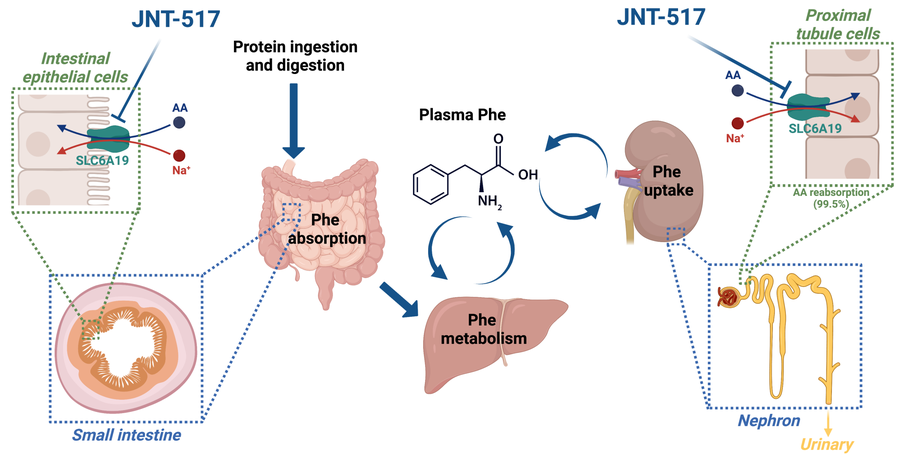
The goal of PKU treatment is to consistently lower blood phenylalanine (Phe) concentrations to avoid neurocognitive and psychological morbidities. First-line treatment for patients with PKU is a low Phe diet that lacks many protein-containing foods and is supplemented by Phe-free medical foods. The diet is very restrictive and requires careful planning and calculation of protein intake.

There are two approved treatments for patients with PKU: Kuvan (sapropterin dihydrochloride) and Palynziq (pegvaliase). Kuvan is tetrahydrobiopterin/BH4, the cofactor for the PAH enzyme that is mutated in PKU, and acts as a molecular chaperone to restore PAH activity. Palynziq is an injectable enzyme substitution therapy.

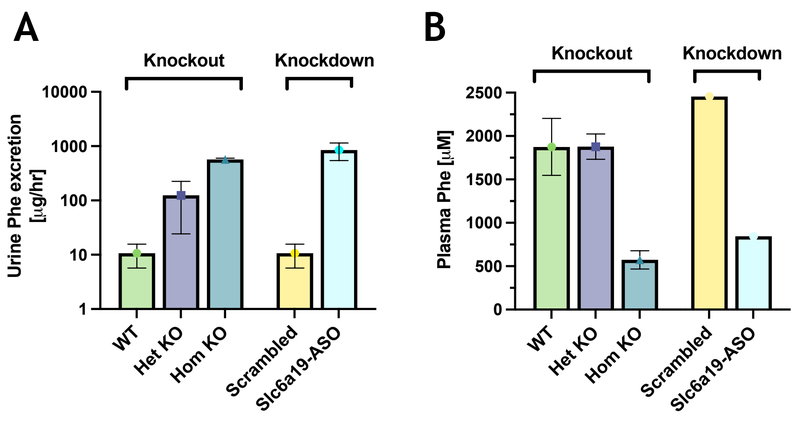
There remains a high unmet medical need for new therapeutic approaches for the treatment of PKU. Jnana Therapeutics is developing **JNT-517**, an oral small molecule inhibitor of Solute Carrier Family 6 Member 19 (SLC6A19) that blocks renal Phe reabsorption and facilitates its excretion, to lower blood Phe levels in PKU patients irrespective of age or background genotype. Preclinical studies in the *Pah*^{enu2} PKU mouse model with a tool inhibitor (JN-170) have demonstrated that **small molecule inhibition of SLC6A19 can reduce plasma Phe levels**. IND-enabling studies to date provide a clear path to the clinic for **JNT-517.**

JNT-517 Mechanism of Action

Dietary Phe is absorbed in the small intestine and enters the bloodstream. The major site of Phe metabolism is the liver, where the enzyme PAH converts Phe to Tyr. The kidney ensures the efficient reabsorption of key nutrients, including amino acids. Under normal conditions, >99% of circulating plasma Phe is reabsorbed while <1% is excreted via urine. SLC6A19 is the major transporter responsible for the intestinal absorption and renal reabsorption of Phe. Individuals with genetic loss of function of *SLC6A19* present with aminoaciduria including elevated urinary Phe excretion, but an otherwise mild phenotype.[1,2] Inhibition of SLC6A19 enhances the urinary secretion of Phe by blocking Phe reabsorption in the proximal tubule, and both genetic loss and inhibition of SLC6A19 reduce plasma Phe levels in a PKU mouse model. **JNT-517** is a potent and selective inhibitor of SLC6A19.



The SLC6A19 Inhibitor JN-170 Phenocopies the Extent of Protection Observed with *Slc6a19* Knockout in the PKU mouse

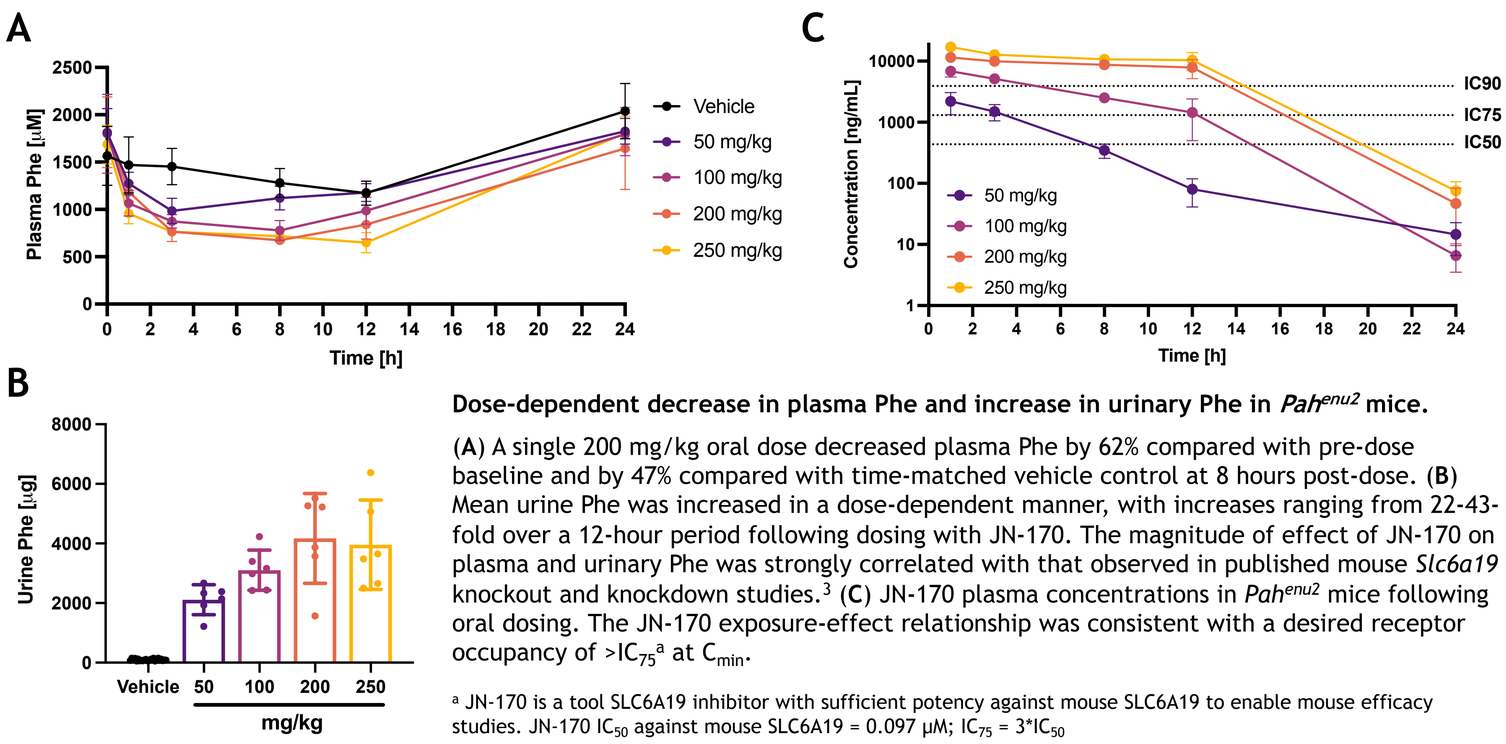


Depletion of SLC6A19 limits Phe accumulation in the *Pah*^{enu2} mouse model of PKU.

(**A**) Urine Phe is significantly increased following *Slc6a19* knockout or knockdown. (**B**) *Slc6a19* knockout or knockdown causes a *ca* 70% reduction in plasma Phe levels.

Adapted from published data by Belanger et al. *JCI Insight* 2018[3]

WT, Het KO, Hom KO: *Pah*^{enu2} mice with 2 (WT), 1 (Het) or no (Hom) functional copies of the *Slc6a19* gene. *Slc6a19*-ASO, antisense oligonucleotide targeting *Slc6a19*

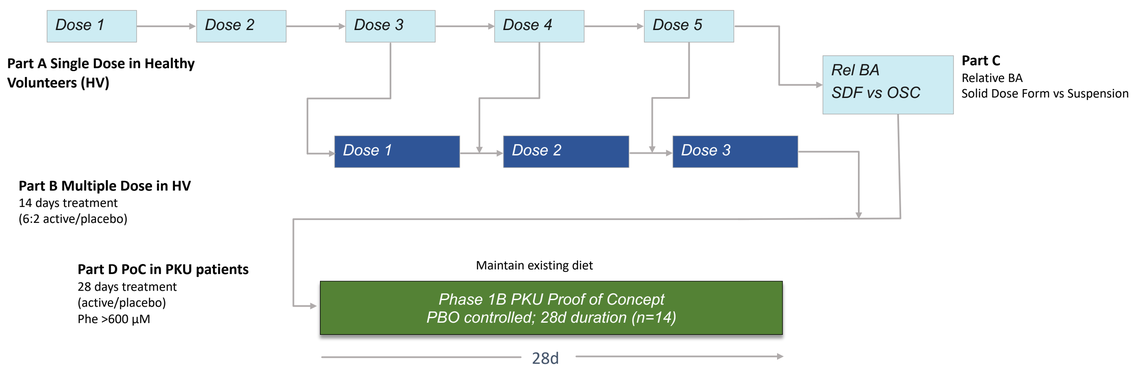


Dose-dependent decrease in plasma Phe and increase in urinary Phe in *Pah*^{enu2} mice.

(**A**) A single 200 mg/kg oral dose decreased plasma Phe by 62% compared with pre-dose baseline and by 47% compared with time-matched vehicle control at 8 hours post-dose. (**B**) Mean urine Phe was increased in a dose-dependent manner, with increases ranging from 22-43-fold over a 12-hour period following dosing with JN-170. The magnitude of effect of JN-170 on plasma and urinary Phe was strongly correlated with that observed in published mouse *Slc6a19* knockout and knockdown studies.[3] (**C**) JN-170 plasma concentrations in *Pah*^{enu2} mice following oral dosing. The JN-170 exposure-effect relationship was consistent with a desired receptor occupancy of >IC_{75}[a] at C_{min}.

[a] JN-170 is a tool SLC6A19 inhibitor with sufficient potency against mouse SLC6A19 to enable mouse efficacy studies. JN-170 IC_{50} against mouse SLC6A19 = 0.097 µM; IC_{75} = 3*IC_{50}

JNT517-101 Clinical Plan



JNT517-101 is a multi-modular Phase 1A/B study designed to assess safety, tolerability and pharmacodynamics of **JNT-517** in Healthy Volunteers and Patients.

Cohorts of Normal Healthy Volunteers will be enrolled in Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) modules to assess the safety, tolerability and pharmacokinetics of different doses of **JNT-517** administered as a suspension over 14 days.

Following completion of the SAD and MAD cohorts a Relative Bioavailability sub-study is planned to compare solid dose form vs suspension.

A small Proof of Concept sub-study is planned to assess safety, tolerability, pharmacokinetics and pharmacodynamics of **JNT-517** tablet vs placebo in participants with classical PKU (plasma Phe levels >600 µM at baseline) over 28 days. Individuals interested in participating in the study can email clinicaltrials@jnanatx.com for more information.

JNT-517 Clinical Candidate Highlights

JNT-517 is a potential first-in-class oral SLC6A19 inhibitor for the treatment of PKU patients independent of background PAH mutation

JNT-517 meets desired characteristics for oral QD or BID therapy

Preclinical data suggests that inhibition of SLC6A19 can achieve a ≥50% reduction in mean plasma Phe

JNT-517 is undergoing comprehensive regulatory safety and toxicology studies, with initiation of Phase 1 clinical studies planned for late 2022

References

1. Seow HF et al. Hartnup disorder is caused by mutations in the gene encoding the neutral amino acid transporter SLC6A19. *Nat Genet*. 2004. doi:10.1038/ng1406
2. Bröer S. The role of the neutral amino acid transporter B^0AT1 (SLC6A19) in Hartnup disorder and protein nutrition. *IUBMB Life*. 2009. doi:10.1002/iub.210
3. Belanger AM et al. Inhibiting Neutral Amino Acid Transport for the Treatment of Phenylketonuria. *JCI Insight* 2018. doi: 10.1172/jci.insight.121762

About Jnana Therapeutics

Jnana Therapeutics is a biotechnology company utilizing their RAPID platform to address well-validated but hard-to-drug targets. Jnana is focused on developing first- and best-in-class therapies to treat a wide range of diseases, including rare genetic diseases, immune-mediated diseases and cancer. Jnana's lead program is a potential first-in-class oral approach, targeting an allosteric site on the phenylalanine transporter SLC6A19, for the treatment of phenylketonuria (PKU). Located in Boston, Jnana brings together scientific leaders in small molecule drug discovery and development, a highly experienced management team and the backing of leading life science investors. For more information, please visit www.jnanatx.com.