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Phenylketonuria pipeline breaks into new modalities

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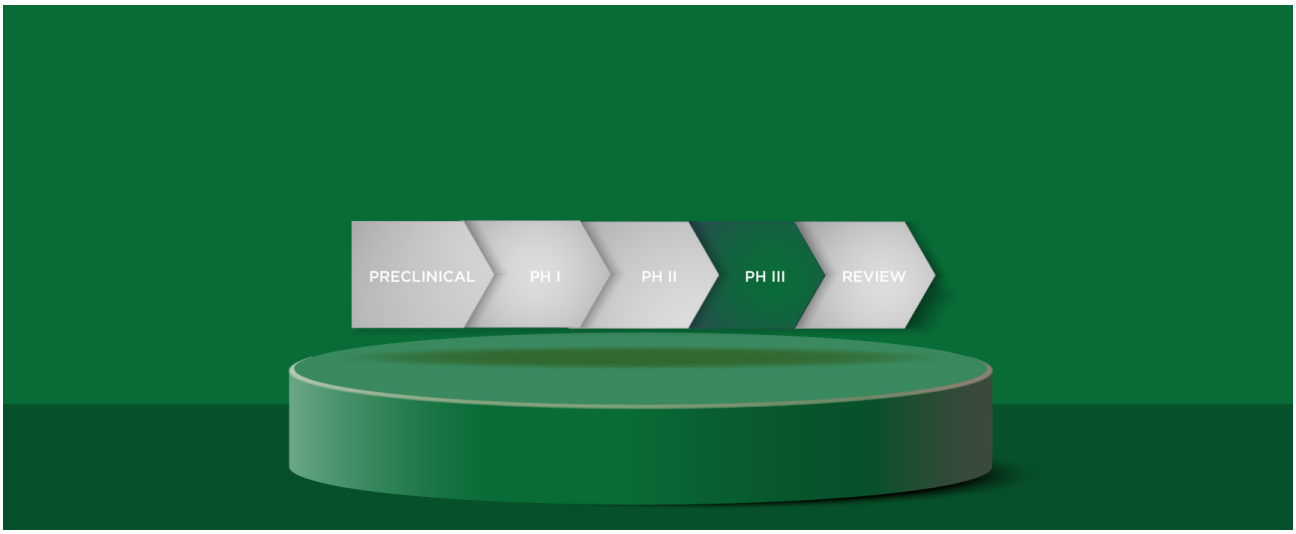

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With Synlogic picking a candidate to advance, the PKU field will soon have two programs in Phase III testing, and coming up behind them are at least 10 more programs spanning multiple therapeutic modalities that go beyond the indication's approved small molecules and enzyme replacement therapies.

Phenylketonuria (PKU) is a rare, inherited metabolic disorder caused by mutations in the gene encoding PAH, an enzyme that normally converts phenylalanine to tyrosine. Mutations in the enzyme result in toxic buildup of the amino acid phenylalanine in the blood, which can affect the brain, leading to intellectual disability.

SYNB1934 from Synlogic Inc. (NASDAQ:SYBX) is the only disclosed bacteria-based treatment in the PKU pipeline. The Nissle-engineered *E. coli* strain expresses PAL — the plant form of PAH — which prevents toxic buildup of phenylalanine by breaking down the molecule into the non-toxic metabolites *trans*-cinnamic acid (TCA) and hippuric acid (HA). SYNB1934 is a second generation, more potent version of the first-generation product SYNB1618.

The company previously told BioCentury it had embedded a head-to-head comparison of the two in its trials, based on which it would choose one for late-stage development. Last month, Synlogic announced results from the Phase II Synpheny-1 study demonstrating a day 14 mean change from baseline in fasting plasma phenylalanine of -20% for SYNB1618 and -34% for SYNB1934. Based on the results, the company said it would advance SYNB1934 into a Phase III registrational study, expected to begin in 1H23.

Ahead of SYNB1934 are two approved drugs and the Phase III candidate sepiapterin from PTC Therapeutics Inc. (NASDAQ:PTCT).

The two approved therapies, Kuvan and Palynziq, are both from BioMarin Pharmaceutical Inc. (NASDAQ:BMRN).

Kuvan provides the PAH enzyme co-factor THB that is required to convert phenylalanine to tyrosine; its therapeutic benefit is dependent on genetic background and only helps a subset of patients. Palynziq is a PAL-based enzyme substitution therapy for adults administered daily via a subcutaneous injection; it has a black box warning of anaphylaxis.

PTC's sepiapterin is a precursor to THB; the company gained the molecule when it acquired Censa Pharmaceuticals Inc. in June 2020. The Phase II trial evaluating sepiapterin for PKU met its primary and secondary endpoints in December 2019, with the therapy reducing blood phenylalanine lower than Kuvan.

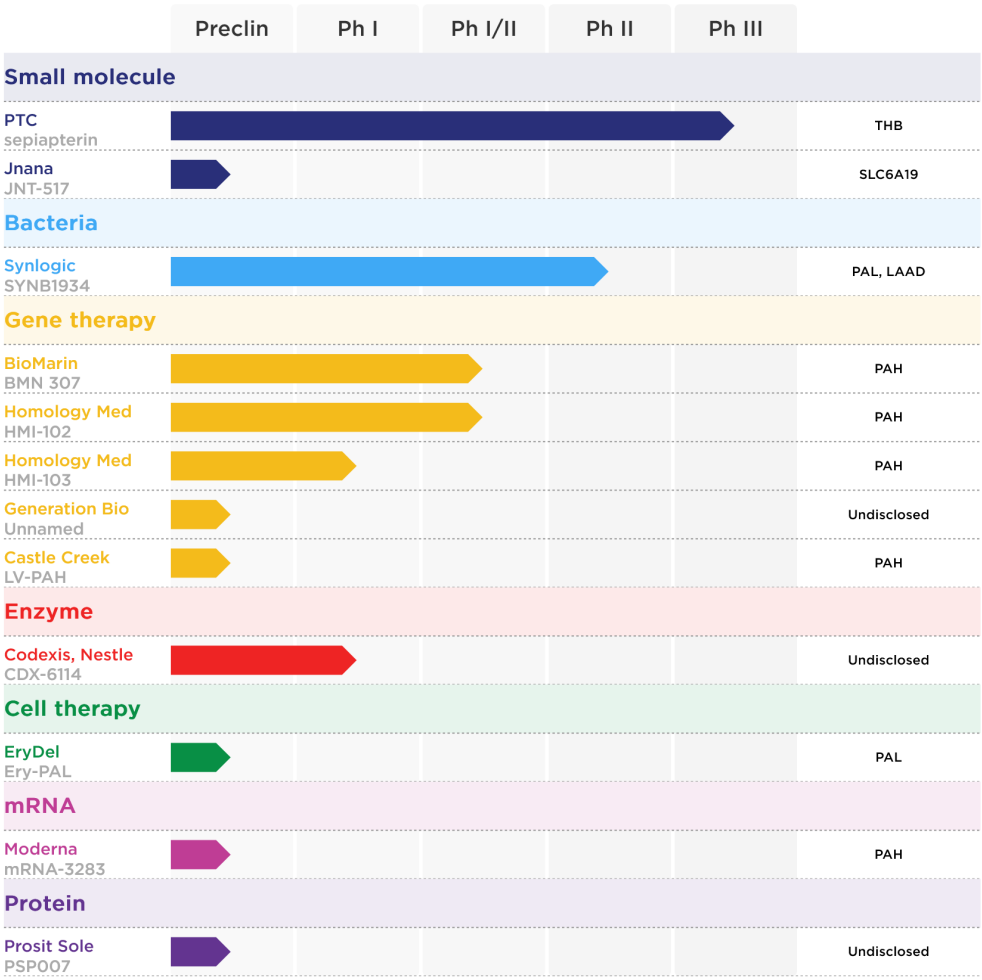
The next-most advanced programs in the PKU pipeline are both gene therapies in Phase I/II testing: BMN 307 from BioMarin and HMI-102 from Homology Medicines Inc. (NASDAQ:FIXX). Both companies are using adeno-associated viruses (AAVs) to deliver a functional copy of the PAH gene.

While Homology's HMI-102 is non-integrating, the company's next-generation candidate HMI-103, which is in Phase I testing, is designed to replace the mutated PAH gene in a patient's genome with a functional copy via homologous recombination. It targets liver cells by using a liver-specific promoter. Two companies — Generation Bio Co. (NASDAQ:GBIO) and Castle Creek Biosciences Inc. — have disclosed preclinical gene therapy programs for PKU.

Other modalities in the pipeline include a preclinical mRNA program from Moderna Inc. (NASDAQ:MRNA) and a new twist on enzyme replacement from EryDel S.p.A. that involves loading autologous red blood cells with PAL.

Chinese biotech Prosit Sole Biotechnology Co. Ltd., which specializes in protein engineering, has disclosed little detail on the IND-stage PKU candidate in its pipeline.

Phenylketonuria pipeline



Source: BCIQ, ClinicalTrials.gov, company websites

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