EP-041

Phase 1/2 open-label study design to evaluate safety, tolerability, and efficacy of SAR444836, an AAV-mediated gene transfer in patients with phenylketonuria

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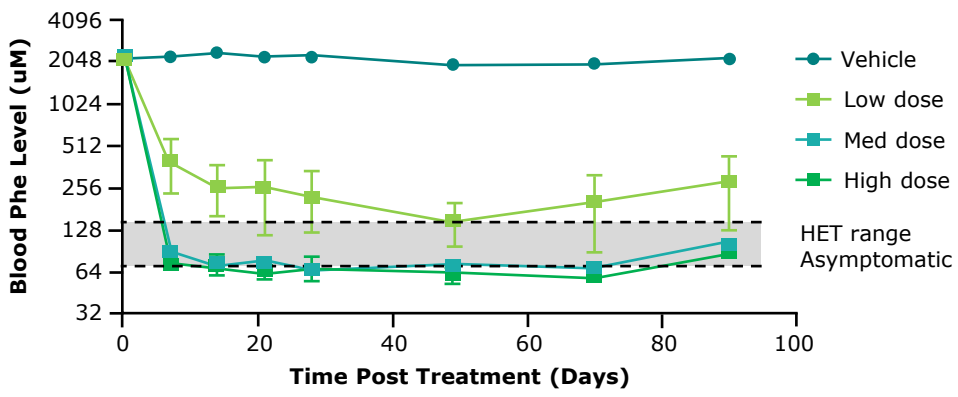
INTRODUCTION

- Phenylketonuria (PKU) is a rare disease caused by pathogenetic variants in the *PAH* gene, leading to deficiency of phenylalanine hydroxylase (PAH) enzyme activity in liver cells. PAH catalyzes the conversion of phenylalanine (Phe) into tyrosine (Tyr), and its deficiency results in elevated levels of Phe in the blood and brain, and subsequent neurocognitive effects.[1,2]
- The standard management for PKU involves lifelong treatment that includes dietary Phe restriction, use of tetrahydrobiopterin (BH4), and/or administration of PEGylated phenylalanine ammonia lyase (Pegvaliase). However, challenges related to strict diet adherence, variable responsiveness to BH4, daily subcutaneous administration, and allergic reactions to Pegvaliase, in addition to suboptimal outcomes, leave an unmet need for improved therapeutic outcomes.[1,2]
- Sanofi is developing a recombinant adeno-associated virus (rAAV)-based gene therapy to restore liver PAH activity to target the fundamental cause of the disease.
- A single systemic administration of rAAVSNY001-hPAH was found to restore liver PAH activity and mediate persistent blood Phe correction in Pah-knockout mice **(Figure 1)**.

Figure 1: Effect of rAAVSNY001-hPAH on Phe Levels in the KO-Mouse Model



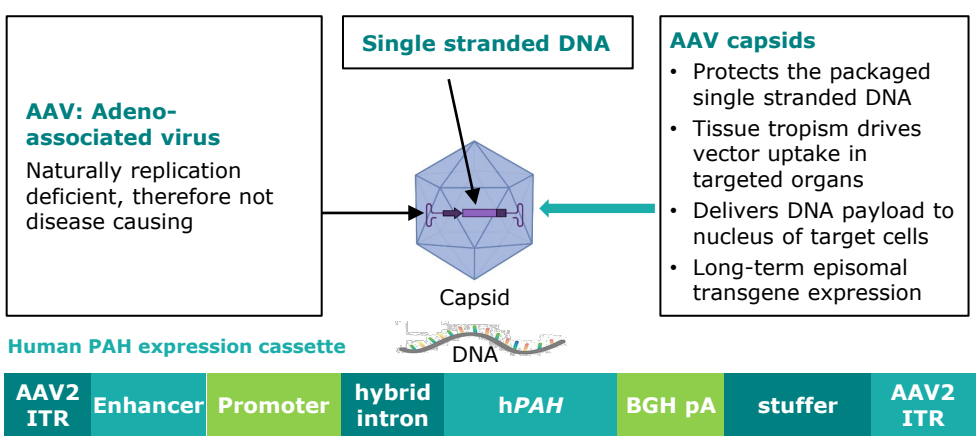
KO, knockout; Phe, phenylalanine.

METHODS

Study Design

- DFI17545 (NCT05972629) is a Phase 1/2, open-label study to evaluate the safety, tolerability, and efficacy of a single intravenous (IV) administration of SAR444836, an AAV vector-mediated gene transfer of human *PAH* **(Figure 2),** in men and women of non-childbearing potential with uncontrolled classical PKU due to PAH deficiency (despite Phe-restricted chronic, stable dietary management or Pegvaliase).

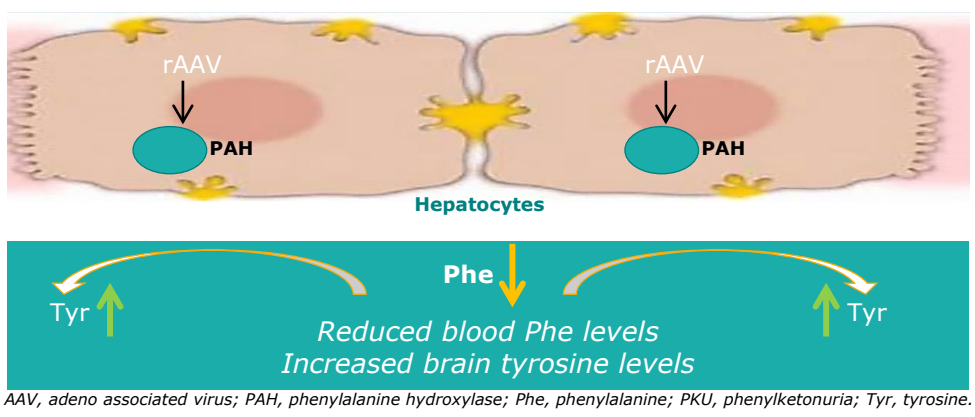
Figure 2: SAR444836 Viral Vector



AAV, adeno-associated virus; BGH pA, bovine growth hormone polyadenylation; DNA, deoxyribonucleic acid; hPAH, human PAH gene; ITR, inverted terminal repeat.

- SAR444836 is designed to target the liver, delivering a functional copy of the human *PAH* gene into hepatocytes using a one-time IV administration **(Figure 3)**.

Figure 3: Therapeutic Strategy of PKU with SAR444836 Viral Vector



AAV, adeno associated virus; PAH, phenylalanine hydroxylase; Phe, phenylalanine; PKU, phenylketonuria; Tyr, tyrosine.

- The study design consists of a dose escalation part (Stage 1A) with three planned dose levels and a dose expansion part (Stage 1B) where a safe and effective dose level identified in Stage 1A will be further tested **(Figure 4)**.
- The study duration is approximately 102 weeks for each patient (either in Stage 1A or Stage 1B) and includes a 6-week screening phase and 96-week follow-up period after SAR444836 administration.

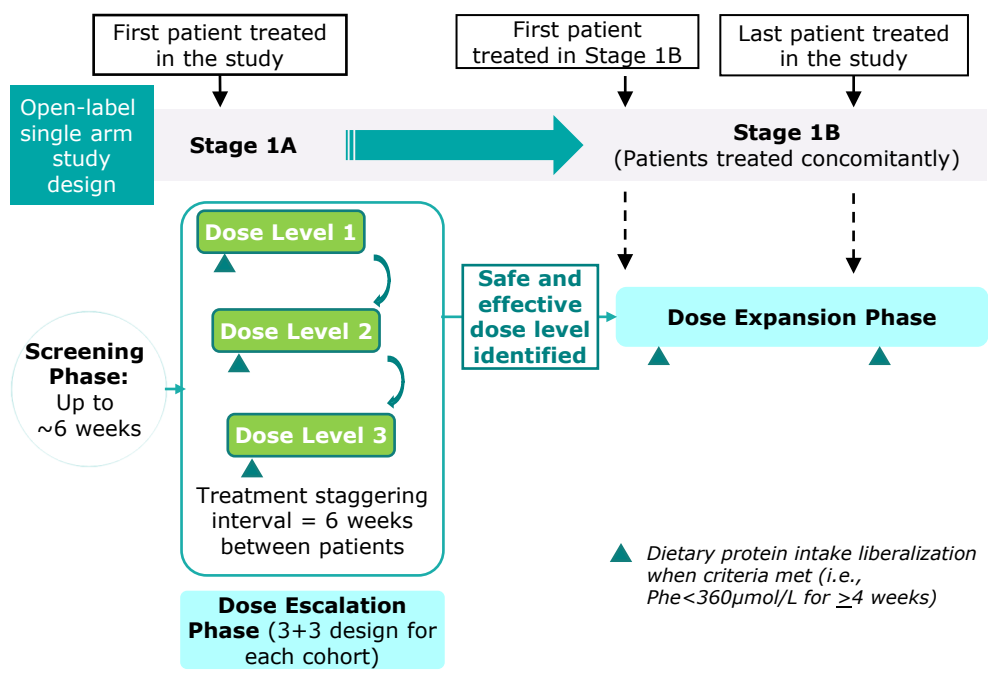
Main Inclusion Criteria

- Patients aged ≥18 to ≤65 years at the time of informed consent.
- Diagnosis of uncontrolled classical PKU due to PAH deficiency.
- Ability and willingness to adhere to the current diet throughout the trial, unless otherwise directed as per protocol.
- Willingness and capability per investigator opinion to comply with study procedures and requirements.

Main Exclusion Criteria

- Presence of neutralizing antibodies against the AAVSNY001 capsid.
- Abnormal liver function tests [alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphate, or total and direct bilirubin >1.5x upper limit of normal]/ significant underlying liver disease such as the diagnosis of portal hypertension, splenomegaly, or hepatic encephalopathy.
- Serum albumin levels below the lower limit of normal of the laboratory or AST-to-platelet ratio index >1.0
- Glycated haemoglobin >6.5% or fasting glucose >126 mg/dL.
- History of active malignancy in the past 5 years, any history of hematologic malignancy, or family history of a cancer predisposition syndrome without negative testing results.

Figure 4: DFI17545 General Study Scheme



Phe, phenylalanine.

Study Endpoints

Primary Endpoint

- Incidence and severity of treatment-emergent adverse events after SAR444836 administration.

Secondary Endpoints

- Change from baseline to Week 24, Week 96 or end of study in:
  - Proportion of patients with sustained Phe plasma level <360 µmol/L, <120 µmol/L, and <600 µmol/L for ≥4 weeks after dietary protein liberalization
  - Change from baseline in plasma levels of Phe, total protein (and Phe) intake, and plasma Phe:Tyr ratios
  - Assessment of the timing and duration of viral vector shedding of SAR444836 in sampling of urine, saliva, and sperm at 4-week intervals following SAR444836 administration.

Exploratory Endpoints

- Change from baseline in quality-of-life measures and neurocognitive assessments on patient-reported outcomes questionnaires.

SUMMARY

- SAR444836, an AAV vector-mediated gene transfer of human *PAH*, is designed to deliver a functional copy of the human *PAH* gene into hepatocytes using a one-time IV administration in adults with uncontrolled classical PKU due to PAH deficiency.
- Targeting the unmet need in the treatment of PKU, this innovative study will investigate whether AAV gene therapy can provide a substantial treatment advantage in PKU.

REFERENCES

1. van Spronsen FJ,et al. *Nat Rev Dis Primers*. 2021 May;7(1):36. **2.** Blau N, et al. *Lancet.* 2010 Oct; 376(9750):1417–1427.

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DISCLOSURES

Fatih Ezgü is an investigator in a Sanofi-sponsored clinical trial, and has been a speaker in a Sanofi sponsored meeting.
David Reiner, Chafik Azizi, Larissa Mege, Anne Ramezi, Pablo Rendo are employees of Sanofi, and may hold shares/stock options in the company.

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