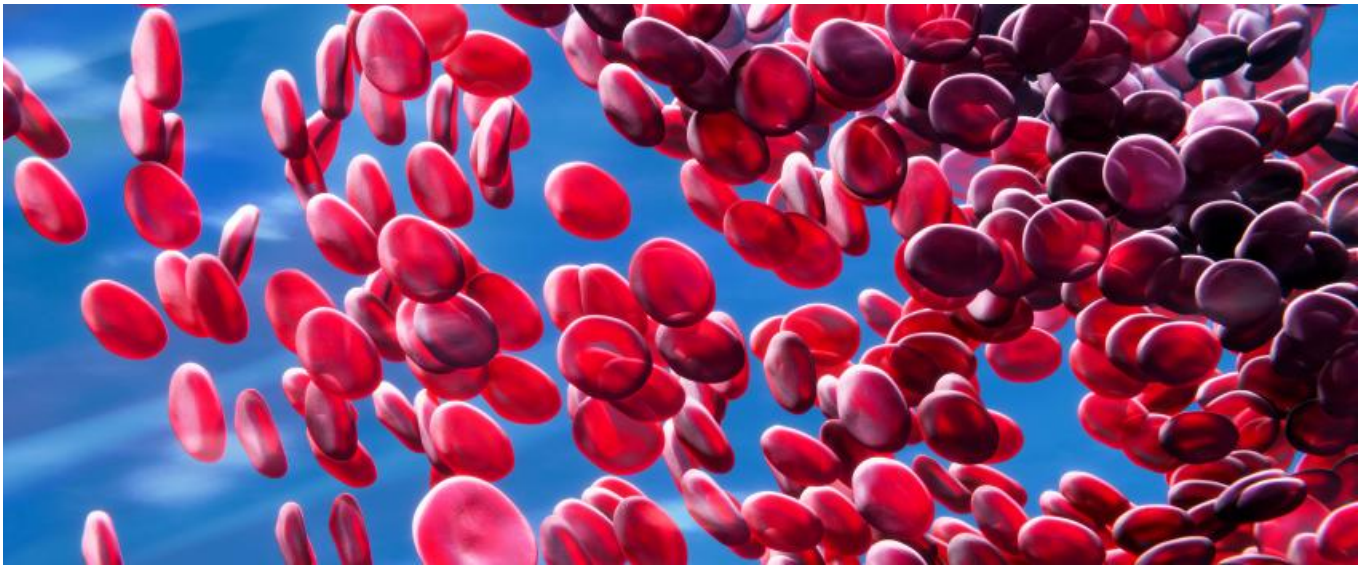
Evaluate Vantage

October 30, 2019

First blood: Rubius approaches its big test

Joanne Fagg



The first clinical data from Rubius Therapeutics will show whether its lead project, RTX-134, has a future. More importantly, the readout is a test of its entire red blood cell engineering approach.

Rubius Therapeutics managed to pull off a $277m float last year despite only having a preclinical pipeline, and investors will soon find out if there is substance behind the hype. By the end of 2019 the company will report its first human data, from four phenylketonuria (PKU) patients in a phase Ib trial of its lead asset, RTX-134.

Rubius's unique selling point is the use of red blood cells genetically engineered to express therapeutic proteins. The upcoming data will therefore have read-across to the rest of the company's pipeline; as well as other rare disease candidates, the group is also developing projects for cancer and autoimmune disorders.

Project	RTX-134
Company	Rubius Therapeutics
Product NPV	$517m
% of market cap	72%
Event	Phase Ib data
Due	By year end

In the case of PKU, RTX-134 is engineered to replace a missing enzyme. The red blood cell delivery system is said to shield RTX-134 from the immune system; Rubius claims that this can avoid immune-driven adverse events seen with conventional enzyme-replacement therapies like Biomarin's Palynziq.

PKU patients have a deficiency in the enzyme phenylalanine hydroxylase (PAH), leading to a build-up of phenylalanine, which is toxic to the brain. RTX-134 aims to address this by delivering a different enzyme, phenylalanine ammonia lyase (PAL), which breaks down phenylalanine into trans-cinnamic acid (TCA).

The single-arm study is set to recruit up to 12 patients with serum phenylalanine levels of 600µmol/l or greater. The data this year will come from part one, testing a single dose of RTX-134; part two will involve multiple doses. Rubius is ultimately targeting once-monthly dosing with intravenous RTX-134.

The results will primarily involve safety and the longevity of the cells, but there should be some early signs of whether RTX-134 is doing its intended job, with data on TCA, a biomarker of activity. More important will be data on phenylalanine levels, which will not be released until next year.

In August Rubius admitted that problems with its contract manufacturer had led to a delay in enrolling into the phase I study; the group had previously hoped to have data from more patients by the end of the year. The company's own manufacturing site is expected to be operational by the end of next year.

Since the delay was revealed Rubius's share price has slipped, but it had already been on a downward trajectory; the group's stock has fallen 66% since its huge IPO, the third biggest of 2018.

The enzyme-replacement therapy Palynziq is forecast to be the biggest PKU product in 2024, according to *EvaluatePharma* consensus, despite its hypersensitivity adverse events. Rubius bulls hope that, if the company's claims are correct, RTX-134 will prove to be safer.

But, even if this is the case, RTX-134 could also eventually go up against gene therapies with an even more convenient "once and done" approach. Examples include Homology Medicine's HMI-102, which has data due from the phase I/II pheNIX study by the end of the year, while last month Biomarin submitted a UK clinical trial application for its candidate BMN 307.

Top five phenylketonuria treatments

			Annual indication sales ($m)			
Product	**Mechanism of Action**	**Company**	**2019e**	**2024e**	**Status**	**Note**
Palynziq	PAL replacement	Biomarin	90	563	Marketed	Once-daily SC, black box warning for anaphylaxis
mRNA-3283	PAH mRNA therapeutic	Moderna	-	400	Preclinical	IND filing expected 2020
Kuvan	Tetrahydrobiopterin (BH4) inhibitor	Biomarin	458	171	Marketed	Must be accompanied by a strict low-protein diet
HMI-102	PAH gene transference	Homology Medicines	-	139	Phase II	Phenix trial data due YE
RTX-134	PAL cell therapy	Rubius Therapeutics	-	138	Phase I	Data from four-patient trial due YE

PAL: phenylalanine ammonia lyase, PAH: phenylalanine hydroxylase. Source: EvaluatePharma.