Evaluate Vantage

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Upcoming events – Biomarin’s achondroplasia hope and Apellis’s clash with Alexion

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Biomarin awaits pivotal data on one of its growth drivers, while Apellis seeks to take off on Pegasus.

Welcome to your weekly roundup of approaching clinical readouts. Biomarin’s recombinant natriuretic peptide vosoritide is far and away the biggest hope for achondroplasia, the most common cause of human dwarfism, with 2024 sales forecasts of $587m according to *EvaluatePharma* consensus.

Topline phase III data from vosoritide’s pivotal trial, in 121 patients aged between five and 18, are expected by the end of the year, and if positive could put the drug on the way to blockbuster status, Leerink analysts believe. The project is expected to become Biomarin's second-biggest growth driver behind another potential blockbuster, the haemophilia A gene therapy valoctocogene roxaparvovec.

There is no approved treatment for achondroplasia other than surgery or growth hormone injections, which are of limited use. Vosoritide is intended to treat the underlying disease, inhibiting FGFR3, overproduction of which shortens patients’ bones.

Vosoritide (formerly BMN111) succeeded in a phase II trial, boosting annualised growth velocity at all doses, though the highest dose, 30µg/kg/day, was not meaningfully better than 15µg/kg/day. Safety, crucially, was clean.

Summary of vosoritide's phase II efficacy data				
Time point	6 months	6 months	12 months	6 months
Cohorts	Cohorts 1 & 2	Cohort 3	Cohort 3	Cohort 4
Dose (µg/kg/day)	15	15	15	30
No of patients	12	10	10	8*
Mean (SD) AGV change from baseline, cm/year	2.3 (1.9)	2.0 (2.0)	1.9 (2.0)	2.1 (2.1)
Mean AGV % increase from baseline	65%	50%	46%	46%
*AGV=annualised growth velocity. *Evaluable patients. Source: company press release.*				

It is the 15µg/kg dose that is being tested in the phase III trial, which is 90% powered to detect 1.75cm/yr annualised growth velocity, against placebo. Phase II showed a 2cm benefit – though that of course was against baseline, so will not have accounted for any placebo effect.

Secondary endpoints include change from baseline in height Z-scores and change in upper to lower segment body ratio, as well as the rate of adverse events. A hit could mean a decent first-mover advantage for Biomarin. The next project in the pipeline, Ascendis Pharma's TransCon CNP, is not expected to be launched until 2023, three years after vosoritide.

If wishes were (winged) horses

Head-to-head trials are always a risky business, and APL-2, the complement factor C3 inhibitor developed by Apellis, will have to distinguish itself against the market leader in paroxysmal nocturnal haemoglobinuria when its phase III trial reports in December.

The Pegasus trial pits APL-2 against Alexion's blockbuster Soliris in 70 patients with PNH who continue to have haemoglobin levels below 10.5g/dl despite being on Soliris.

Pegasus's dosing regimen is complicated to say the least. All 70 patients in the trial must have already been taking Soliris for at least three months. They then all start taking subcutaneous APL-2 as well, at 1,080mg twice daily, for a 28-day run-in.

At that point, the trial population splits. Half are randomised to APL-2 monotherapy at the same dose. The other half continue to receive their pre-screening dose of Soliris, without APL-2. The primary outcome, improvement in haemoglobin levels from baseline, is measured at 16 weeks after randomisation.

The fact that all subjects will at some point have got Soliris at various points in the trial could make extrapolating APL-2's effect tricky. Analysts from Evercore ISI expect the topline Pegasus data to be positive, but note that C3 inhibition could increase the risk of infection.

If the study does hit, and safety is acceptable, Cantor Fitzgerald cites a conservative scenario in which Apellis seeks a label covering patients with haemoglobin levels below 10.5g/dl – around half of the PNH population. The company also has an ongoing phase III study in Soliris-naive patients, Prince, which could lead to expanded approval in the future.

But the sellside as a whole remains unconvinced. In terms of 2024 sales forecasts, as compiled by *EvaluatePharma*, APL-2 is a distant third to Soliris and its potentially even more successful follow-on Ultomiris. Still, some analysts consider that Alexion's play for Achillion is a defensive move in the face of the competitive threat from Apellis.

Top five PNH drugs in 2024								
		Annual sales for PNH ($m)						
Product	**Company**	**2018**	**2019e**	**2020e**	**2021e**	**2022e**	**2023e**	**2024e**
Ultomiris	Alexion Pharmaceuticals	-	275	777	846	988	1,077	1,075
Soliris	Alexion Pharmaceuticals	1,723	1,937	1,557	1,329	1,217	1,083	1,032
APL-2	Apellis Pharmaceuticals	-	-	-	4	34	77	134
ACH-5228	Achillion Pharmaceuticals	-	-	-	-	17	55	83
RG6107	Roche	-	-	-	-	25	44	66
PNH=paroxysmal nocturnal haemoglobinuria. Source: EvaluatePharma.								

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