Evaluate Vantage

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Upcoming events – Soleno has a date with Destiny while Arbutus tries again

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Solena is poised to show whether it can sate genetically driven hunger, while the hepatitis B wannabe Arbutus needs to put previous clinical failures behind it.

Welcome to your weekly roundup of approaching clinical readouts. The only pharmacological product approved specifically for Prader-Willi syndrome, the genetic condition characterised by insatiable hunger, or hyperphagia, is growth hormone. Attempts to develop a new Prader-Willi medicine, most notably those by Zafgen, have so far met with failure.

Soleno Therapeutics has not been put off. Topline phase III data on its only asset, a controlled-release form of diazoxide choline, are expected by mid-year. Diazoxide, a potassium channel activator, was first approved in 1973 as a treatment for hypoglycaemia caused by overproduction of insulin, for example in patients with islet cell malignancies.

The rationale for its use in Prader-Willi is that, according to Soleno, it can open potassium channels in a particular type of neuron in the hypothalamus, interrupting synthesis of an appetite-stimulating neuropeptide that is overproduced in Prader-Willi patients.

The randomised Destiny Prader-Willi study is testing once-daily doses of 75-450mg in 100 patients with the condition, aiming to decrease hyperphagia-related behaviour versus placebo.

In the uncontrolled stage of phase II trial diazoxide choline reduced hyperphagia versus baseline in 11 obese Prader-Willi subjects; beating placebo will clearly be harder to achieve.

On safety Soleno can point to decades of data from diazoxide's use in hypoglycaemia. But it is not a wholly clean drug; its label lists sodium and fluid retention as a frequent and serious adverse reaction.

Sellside forecasts have diazoxide choline leading the market in 2024. Importantly, though, phase II data from the phase II/III Zephyr trial of Millendo Therapeutics' livoletide are also due in the first half. Leerink analysts expect the trial to succeed, with moderate changes in hyperphagia and no safety concerns, and add that if the phase III part of Zephyr is also a hit the data could be registrational.

The Prader-Willi outlook				
		Annual indication sales ($m)		
Project	**Company**	**2020e**	**2022e**	**2024e**
Diazoxide choline CR	Soleno Therapeutics	–	127	361
Livoletide	Millendo Therapeutics	–	23	188
Genotropin (growth homone formulation)	Pfizer	0.4	0.4	0.4
Source: EvaluatePharma.				

Meanwhile, having abandoned two previous hepatitis B projects – for lack of safety and efficacy – Arbutus desperately needs its next wave of contenders to shape up. The first clinical data on what is now its lead compound are due in the coming weeks; the news might come with fourth-quarter earnings on March 5.

AB-729 is the project in focus, a subcutaneously administered RNAi therapeutic said to target all four major hepatitis B transcripts that the virus uses to replicate and rebound. One of these is called surface antigen, or HBsAg, and developers are trying to show that their respective projects can suppress the levels of this biomarker.

Arbutus is running a phase Ia/II trial with AB-729. Results from a single ascending dose will be seen initially, with data on multiple ascending doses following in the second half; the first readout should provide a decent insight into what this project might be capable of.

Baird analysts reckon that a 0.5 log decline in HBsAg would “substantially derisk” AB-729 versus other RNAi approaches. Should the second-half readout manage to show a greater than 1 log decline, AB-729 would start to look very promising, they believe.

As an aside, the trial only appears to be registered in New Zealand.

Arbutus is trailing other RNAi developers seeking to find a functional cure for hepatitis B, most of which have already secured big pharma partners; Arrowhead is partnered with Johnson & Johnson, while Roche signed up Dicerna last year.

As well as dispelling doubts over earlier pipeline failures, with this next update Arbutus must show that it can stay in this race. With so much catching up to do, less than spectacular data might struggle to capture attention.