Evaluate Vantage

May 26, 2022

The lowdown on high blood pressure

Amy Brown

After Idorsia's tease in resistant hypertension, data will soon emerge on other advanced assets, including long-acting RNA-based approaches.

Idorsia claimed a win for its Johnson & Johnson-partnered blood pressure project earlier this week, though without any actual data the real potential of aprocitentan remains hard to gauge. The phase 3 asset is one of biopharma's most advanced for resistant hypertension, so the results will set a bar for those coming behind.

Several groups will report mid-to-late stage data in the coming months, including Cincor, which managed to pull off one of 2022's few IPOs, and Ionis, which has a once-weekly antisense agent. Clinicians struggling to treat patients with stubbornly high blood pressure will be watching with interest, as will any large developers with an eye on this potentially large market.

The sum that J&J paid to secure rights to aprocitentan illustrates what projects might be worth. Back in 2017 the pharma giant handed over a $230m fee to exercise its option over the asset, which was then in phase 2, in a deal that also involved hefty royalty terms.

True, Idorsia's chief executive, Jean-Paul Clozel, has long proved himself a canny negotiator – his sale of Actelion to J&J for $30bn was something of a masterclass. But it is also true that cardiology is a therapy area that tends to see large, late-stage deals – exactly the territory that several of these assets are approaching.

Whether J&J is still interested in aprocitentan in light of the Precision data remains to be confirmed. Idorsia promised full disclosure at a conference later this year, and this detail is crucial to determine whether the project has legs.

Aprocitentan, a dual endothelin antagonist that hits A and B receptors, represents a novel approach; most existing blood pressure drugs, and pipeline projects, come at the problem via the renin-angiotensin-aldosterone system (RAAS). Endothelin antagonists are used in pulmonary arterial hypertension – see J&J's Actelion-derived Opsumit – but toxicity has derailed this mechanism in systemic hypertension.

For example, Gilead abandoned darusentan, an endothelin type A receptor antagonist, more than a decade ago largely because of high rates of oedema. This affected almost a third of patients in pivotal studies and caused a high rate of withdrawals, an issue that will be watched closely when aprocitentan data are finally unveiled.

Tackling treatment-resistant hypertension: selected mid-late stage projects			
Project	**Company**	**Mechanism**	**Status**
Aprocitentan	J&J/Idorsia	Endothelin A & B receptor antagonist	Ph3 toplined positive May 2022
Firibastat	Quantum Genomics	Aminopeptidase A inhibitor	Ph3 Fresh study in treatment-resistant hypertension due Oct 2022; extended treatment Refresh trial due mid-2023
Baxdrostat (CIN-107)	Cincor	Aldosterone synthase inhibitor	Ph2 data due H2 2022 from Brighhtn trial for treatment-resistant hypertension and Halo in uncontrolled hypertension
IONIS-AGT-LRx	Ionis	Angiotensinogen antisense	Ph2 Astraas trial in uncontrolled hypertension to report H2 2022
Zilebesiran	Alnylam Pharmaceuticals	Angiotensinogen RNAi therapeutic	Ph2 monotherapy Kardia-1 trial to report mid-2023; data from ph2 add-on Kardia-2 trial due mid-late 2023
ION904	Ionis	Angiotensinogen antisense	Ph2 trial in uncontrolled hypertension recruiting
Source: Evaluate Pharma & company statements.			

Next to produce pivotal data will probably be the tiny French developer Quantum Genomics, with firibastat. This project is said to work by blocking the production of angiontensin in the brain, but earlier data underwhelmed, and the company's €63m ($68m) market cap suggests that hopes are low.

If market caps are anything to go by, Cincor is considered a better bet. The US biotech, which is worth around $550m, has largely managed to hang on to its valuation since floating in January, an impressive feat in the current climate.

Crucial readouts are looming later this year from two phase 2 studies of baxdrostat, which is proposed to work by inhibiting aldosterone synthase, the enzyme responsible for making the blood pressure-regulating hormone aldosterone. As a one-asset company Cincor represents something of a pure bet on this mechanism; the group licensed baxdrostat from Roche in 2019 alongside a series A venture round.

Going long

Other novel projects use RNAi or antisense, and here Alnylam and Ionis are taking different approaches to development.

Ionis will be first to report with its once-weekly antisense asset IONIS-AGT-LRx, and safety is going to be closely watched. IONIS-AGT-LRx works by inhibiting angiotensinogen in the liver, a target that sits right at the top of the RAAS pathway, upstream of widely used drugs like ARBs and ACE inhibitors.

The company is already taking a second-generation molecule into phase 2. A decision on which is the best project, and the next steps, will be made next year, Ionis executives said earlier this month.

Alnylam's RNAi therapeutic zilebesiran also targets angiotensinogen, and the phase 2 Kardia programme should start reading out next year. The company seems to be aiming at the milder end of hypertension, however, where the need for new agents is less clear.

Cheap, generic pills prove effective for the vast majority of patients, with up to a fifth failing to respond adequately. Resistant hypertension is defined as high blood pressure despite the use of at least three blood pressure-lowering drugs, with different mechanisms, at their maximum doses.

These poorly managed patients are at a significantly increased risk of cardiac problems, stroke and kidney damage – a niche where an expensive, novel therapy could presumably justify its existence more easily.

Zilebesiran will be infrequently dosed, possibly once or twice a year, so there are convenience and compliance arguments to be made here. But there are plenty of examples of novel agents that have struggled to make headway on this basis, and it could be considered foolhardy if Alnylam pushed into pivotal trials without also targeting the hypertension patients that have run out of options.

More from Evaluate Vantage

Evaluate HQ
44-(0)20-7377-0800

Evaluate Americas
+1-617-573-9450

Evaluate APAC
+81-(0)80-1164-4754