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In Alnylam's Search For A Mass-Market Treatment, A Twice Yearly Blood Pressure Injection Could Fit The Bill

Crucial Phase II Readouts This Year

by Andrew McConaghie

Alnylam is using its RNA interference technology to target hypertension, which could create a true mass-market cardiovascular blockbuster drug for the firm – but upcoming Phase II data will need to be compelling.

Alnylam is recognized as a pioneer of the RNA interference (RNAi) gene-silencing field, but so far it has not been able to produce an out-and-out blockbuster from its innovative platform, instead having to fight it out in a competitive and niche ATTR amyloidosis market with drugs such as OnPattro (patisiran).

The Cambridge, MA-based biotech is, however, looking to broaden the range of its RNAi medicines, and its potential twice-yearly injection to treat high blood pressure, zilebesiran, is one of its most highly rated development candidates.

Alnylam envisages the drug either as a monotherapy to replace current standard of care in hypertension (dominated by generic pills) or, more likely, as a combination with these therapies – and the moment of truth from two Phase II studies of the the drug is approaching.

The company has just published full Phase I results in the *New England Journal of Medicine*, updating early readouts which showed the drug to be safe and effective.

Patients receiving the highest dose (800mg) tested achieved a mean 22.5mmHg of systolic blood pressure (SBP) and 10.8mmHg diastolic blood pressure (DBP) lowering, with 24-hour ambulatory blood pressure monitoring, at week 24, the drug's effects having increased steadily over this

period.

Those encouraging results need to be mirrored in two larger Phase II studies: the KARDIA-1 (monotherapy) and KARDIA-2 (combination therapy) results are expected in mid-2023 and near year-end respectively.

The combination study, in particular, is seen as crucial for the candidate, as physicians are thought most likely to add the twice-yearly injection into existing standard of care regimens in patients still missing their target blood pressure.

Analysts at UBS forecast that the drug could achieve annual sales of $2.5bn by 2032 but currently assign a 50% success rate to the program. Success would entail showing significant extra benefits for patients with monotherapy or combination therapy, or the product would otherwise face a forecast downgrade, or even see plans for Phase III development scrapped.

There is a clear market opportunity for Alnylam, as hypertension remains the leading cause of premature death, cardiovascular disease and chronic kidney disease worldwide. It affects around 100 million people worldwide, but nearly half of patients fail to achieve guideline-recommended blood pressure targets on existing drugs, with compliance problems a significant issue.

Current standard of care includes thiazide diuretics, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and single-pill combinations of these.

Most of these drugs work by targeting downstream mediators of the renin-angiotensin-aldosterone system (RAAS), which plays a central role in controlling blood pressure. Alnylam's subcutaneously administered RNAi drug acts further upstream by silencing synthesis of angiotensinogen in the liver.

Phase II Studies

The KARDIA-1 monotherapy trial is looking at four dosing schedules (150mg every six months, 300mg every six months or every three months, and 600mg every six months).

The study's primary efficacy endpoint is change from baseline SBP after three months of treatment. Key secondary and exploratory endpoints include blood pressure reduction at six months, time-adjusted change in blood pressure, and change in day-time average and night-time average blood pressure.

The current benchmark of standard treatments is SBP reduction of around 4-16mmHg, depending on the drug class. Thus key opinion leaders spoken to by Barclays analysts this month (as part of a deep dive investor note into the candidate) believe KARDIA-1 would need to achieve

around 20mmHg unadjusted or 10mmHg placebo-adjusted SBP reduction, with around 50-80% of patients being well-controlled on study.

For KARDIA-2, the KOLs said a SBP/DBP reduction of 30/15mmHg with around two-thirds of patients in the normotensive range for combination therapies would be needed on top of standard therapy in order to be potentially practice-changing.

This study is looking at a combinations with a variety of standard-of-care treatments. Alnylam has indicated its expects zilebesiran to demonstrate extra benefits, which would vary according to the combination.

For those taking the drug in combination with indapamide, its expects a ⩾10mmHg reduction, an extra ⩾8mmHg for those taking amlodipine, and additional reduction of 5-6mmHg for a olmesartan cohort.

There remains a question about how far into frontline treatment Alnylam could take zilebesiran. The answer to that question is crucial to the drug's long-term prospects, as the more limited field of resistant hypertension treatment is being pursued by competitors, including *Idorsia* with its Phase III asset aprocitentan and *Novartis* with its XXB-750 in Phase II.

Alnylam is keen to talk up its candidate’s good safety profile, and its potential to help address the common compliance problem thanks to its twice-yearly administration. The company has also forecast that a 5mmHg reduction in patients could translate into a reduction in heart attacks and strokes of up to 10%, though this would have to be addressed in a later large-scale Phase III cardiovascular outcomes study.