Evaluate Vantage

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Akero’s imperfect Harmony

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An apparent hit in Nash has more than doubled the group’s market cap. But are the data all they seem?

Clinical successes in Nash are rare occurrences, so the 115% lift in Akero Therapeutics’ stock this morning, on a phase 2 hit with its FGF21 analogue efruxifermin, is not to be wondered at. The data look convincing at first glance, and the company is starting to plan its registrational trial programme.

But the primary endpoint analysis, which just squeaked into statistical significance, was flattered by the exclusion of the handful of patients who dropped out of the trial. The company admitted today that, had it done a more rigorous intent-to-treat analysis of the data, the study would not have been quite such a slam-dunk.

Topline data from Harmony, a 24-week phase 2b study, showed both doses of efruxifermin hitting the primary endpoint of improvement in at least one stage of fibrosis without worsening steatohepatitis. The trial had signed up patients with pre-cirrhotic Nash and fibrosis stage 2 or 3.

Decent results were seen in Nash resolution without worsening liver scarring, and impressively 41% of those treated with the higher dose had both Nash resolution and improvement in fibrosis.

Harmony – endpoints at wk24			
	Placebo	**Efruxifermin 28mg**	**Efruxifermin 50mg**
N for safety analysis	43	40	43
Discontinued for adverse events	0	2	3
Discontinued for administrative reasons	1	0	5
Declined second biopsy	1	0	1
N for primary endpoint analysis	**41**	**38**	**34**
Mean pts seeing improvement in at least one stage of fibrosis without worsening Nash	20%	39%	41%
P value vs placebo		<0.05	<0.05
Mean pts achieving resolution of Nash without worsening of fibrosis	15%	47%	76%
P value vs placebo		<0.01	<0.001
Mean pts seeing Nash resolution AND improvement in at least one stage of fibrosis	5%	29%	41%
P value vs placebo		<0.01	<0.001
Source: company release.			

All highly satisfactory – until one looks at the discontinuations. It is not so much efruxifermin's toxicity itself, although there were two dropouts in the 28mg dose arm, and three in the 50mg cohort (one of the latter discontinuations was reported to be unrelated to study drug). It is more the fact that Akero removed these subjects from its primary endpoint analysis.

In total 11 patients – 10 treated with efruxifermin and one given placebo – left the study before completion. The six who did not discontinue owing to side effects left for "administrative reasons", Akero said. Two further patients declined to undergo a second biopsy. All these subjects were excluded from the efficacy analysis.

An intent-to-treat analysis including the dropouts would mean that "the percentages would come down, but they would remain statistically significant for three of the four [endpoints]", Andrew Cheng, Akero's chief executive, said on a conference call today.

"We lose the 50mg on an ITT basis, and you can see why that makes sense given the slightly higher number of dropouts," he admitted.

Next up

Mr Cheng said most of Akero's competitors' phase 2 Nash trials used the subset of patients who yielded liver biopsies as the primary endpoint, rather than an ITT analysis. And clearly the group feels that the Harmony data warrant a move into phase 3. It is "finalising the design" of a programme of three pivotal trials to start next year.

Before that, though, the phase 2b Symmetry trial in biopsy-confirmed Nash patients with compensated cirrhosis will report. Data from this, and a 12-week expansion cohort examining efruxifermin on top of GLP-1 therapy in patients with F1-F3 fibrosis, are expected next year. Investors will surely be watching the statistical analyses closely.

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