FROM DROP TO DOUBLE: AKERO'S SURGING STOCK

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Rod Wong in 2023: "This morning, there's news from one of the NASH companies that we'll touch on: Akero. Came out at 7 in the morning. And I said, 'well, I could do a run through for our 150 LPs, but I think they would prefer, and I would prefer, if I just traded this stock.' So, for the last hour and a half I've been trading Akero, and if that costs me in terms of my eloquence, so be it."

Rod Wong: I'm Rod Wong, Managing Partner and Chief Investment Officer at RTW, and I'm also today's RTW Podcast host. So, what you just heard was a clip of me from our 2023 RTW Investor Day. That morning, Akero's stock was down about two-thirds on a trial miss.

It was a scary moment for the company. It also happened to be the day that RTW first became a shareholder. A lot has happened since then. The company today is in a position of strength, and so I have the privilege of welcoming the CEO of Akero, Andrew Cheng. Andrew, thank you for joining us.

Andrew Cheng: I'm happy to be here.

Introducing Akero Therapeutics and MASH

Rod Wong: Your company, Akero, you're one of the most advanced companies developing therapies for MASH. So, where I thought we could kick off was to give a little bit of context to our listeners about MASH as a disease. MASH is short for metabolic dysfunction-associated steatohepatitis, which is a mouthful.

I think in non-jargon, that's fatty liver. It progresses to fibrosis, which is scarring, and then ends in cirrhosis, which is liver failure.

So, you have started two phase-three trials: one in F2-3 and another in F4 patients a year-plus ago. Can you tell me what F2-3 and F4 patients are, and the difference between these two types of patients?

Andrew Cheng: Let's start with the F4. These are people who are what they call cirrhotic, which means it's a situation where the liver is heavily scarred with fibrotic tissue. So, when one thinks about it, one could think about a sponge which is dry.

And that's how it's hard and rigid. Your liver should be like a wet sponge. And that is that it's supple and it's flexible, but it's not full of fibrous tissue.

“Those patients, unfortunately, who have cirrhosis due to MASH have about a 50% mortality rate at five years. "

Their lifespan is greatly shortened, unfortunately. We were interested in studying that population. And then the other population, which is called F2 or F3, is called pre-cirrhotic. So, they have advanced MASH, F3 being more advanced than F2, but they are not yet cirrhotic.

Rod Wong: And your product, efruxifermin, targets something called FGF21. That is different from Rezdiffra, which is the first approved drug that we have. And that targets the thyroid hormone receptor. What got you excited about the mechanism that you guys are going after?

Andrew Cheng: Efruxifermin as an FGF21 is attractive to us because it has a dual mechanism of action. It has two ways that it works. One is through directly inhibiting fibrosis, meaning that it inhibits the deposition of new collagen fibers.

So it's what we would call directly anti-fibrotic. The other mechanism is one that's more common. It's anti-steatotic, which really means it's good at removing liver fat overall.

That removal leads to secondary healing, but it takes longer to achieve secondary healing versus something that's directly anti-fibrotic.

Discussing Akero’s Trials and Setbacks

Rod Wong: With that background, I wanted to jump to that day that I led off with, the day that Akero's stock dropped in October of 2023. This was the day that you had a 36-week readout of a Phase 2 trial that you were running in these F4 patients.

The trial is called SYMMETRY, I believe. The topline summary of it was that the drug reduced fibrosis by 22 to 24% versus the placebo arm, which was 14%. That wasn't statistically significant. So, I'm going to give my impression of what investors thought of that data, which is that if you saw the same thing in a Phase 3 trial, that there was a good chance that those Phase 3s also wouldn't be statistically significant.

After you had that data in hand, you went ahead and started two Phase 3 trials, which is a significant commitment. What gave you the confidence, when investors didn't have it at the time, to move forward with those Phase 3s?

Andrew Cheng: You're right, Rod. That was a difficult day.

But at the same time, when we started looking at the data and speaking with other hepatologists who were in the field, they were very, very encouraging. I think it's helpful for the audience to set the stage for NASH therapies in cirrhosis.

And it's actually pretty easy. Regardless the mechanism, regardless the company, regardless the duration of the trial, none of them had ever worked. And that is, unfortunately for patients, a tremendous loss that these patients who have a five-year, 50% mortality, don't have a trial that's ever been successful, regardless of the stage.

Our hepatologists who help us and guide us, when they looked at the data, they were very encouraged. That is, that they saw hope, quite honestly, because these were the best results. You're correct, they were not statistically significant.

But they opened the door of possibility for, perhaps, with longer-term dosing of these patients, beyond 36 weeks, that we might have a different result. It was their guidance and their encouragement that gave us confidence to start a Phase 3 study in cirrhosis.

Also recognizing that the Phase 2 study SYMMETRY, which had 36-week results, was designed to have a later end point at two years.

It's a decision we made quite a while ago. We decided to look at two endpoints, both at 36 and at two years, primarily because we weren't sure how long it would take, since every other trial had been unsuccessful.

Rod Wong: What was that moment like for you, as the CEO, the leader of the company, and really just as a person?

Andrew Cheng: We did see very encouraging signs. But it was a difficult day.

We obviously were hopeful, based on some very, very small Phase 2a data, that nine months would be an appropriate time to look at the cirrhotic patients. We were not correct when it comes to being statistically significant.

Whenever you design trials, you certainly don't design them to fail. And so we were hopeful, based on the previous data, that it would be successful.

Rod Wong: Earlier this year, your belief was rewarded. You reported that longer-term follow-up data from the same study, 60 additional weeks. And with that additional time, the difference versus placebo, basically, roughly doubled. It was statistically significant. And the result was your stock also doubled. Now you are the only MASH company, I believe, that decided to run a Phase 2 study out that far, with that much follow-up. In hindsight, it's obviously an incredibly smart, wise decision that you made. Why did you decide to study it out that far?

Andrew Cheng: Truthfully, we weren't certain what the correct window and duration should be. We'd like to think that we're correct all the time, but clearly no one's correct all the time and so, we wanted to give ourselves every chance for success.

And we also wanted to learn as much as possible about efruxifermin. We wanted to have more data both for efficacy and safety, and that's why we wanted to provide the best chance, frankly, for the drug and for the patients in the study to benefit.

Rod Wong: It was a brilliant decision. I think it's probably fair to say that, prior to the launch of Madrigal's Rezdiffra, it was a major debate as to whether MASH was a blockbuster market or not.

Becoming pioneers in pre-cirrhotic and cirrhotic treatment

Rod Wong: And I think it's also fair to say that now that we're one year into their launch that that debate is being settled. Now, you're obviously competing to be the first drug approved for F4s or these cirrhotic patients that we've been talking about. Madrigal is also pursuing that population. And you're looking to join them to be hopefully the second drug in F2, F3s: the pre-cirrhotics. Now, if you are both successful in those two populations, how do you think that drugs are going to coexist in each of them? Are investors that you talk to, are they missing something when it comes to this?

Andrew Cheng: When one looks at the number of patients who are afflicted with MASH, whether it's pre-cirrhotic or cirrhotic, they're not all the same. They have various distinctions between them. And I think the opportunity to have more than one drug either in the pre-cirrhotic or cirrhotic category really benefits patients and companies, because it gives the opportunity for a degree of personalization when it comes to therapy of choices, which is true in just about every other category that doctors and patients have options.

That's never a negative to be able to provide that in the MASH space.

Rod Wong: You joined the company before it went IPO. And in that time, you've managed it in a biotech bull market. But that was before people really believed in MASH, or there was a decent amount of skepticism. So, I'll call it a MASH bear market. And now today we're in a biotech bear market and a MASH bull market, so the opposite is true. Now, MASH is a disease that requires large clinical trials, that means it requires a lot of capital. How have you navigated through these different periods of time and how challenging was it?

Andrew Cheng: It was very challenging. I wouldn't describe it in any other way.

“It's very difficult in the bear market times when you struggle with investor support and also marshalling your team, your company, to continue moving forward in that headwind situation.”

At the same time, fields take time to mature. And we were blessed with having investor support that was with us from the beginning, and most of the key investors are still with us today.

The ability to raise capital clearly is aided by having good clinical trial results. So, to some degree, we set the drug up for success, but it took time to realize that success because of the long duration of the studies and the time necessary to raise the capital.

Challenges of being a biotech CEO

Rod Wong: Our audience, we have a lot of folks who, they know biotech in terms of the ups and downs that they see around binary events. And they also appreciate the importance of great medicines that help patients. But they definitely do not live your life, right, as a CEO leader trying to get these medicines across the finish line. So, do you happen to have any words of insight that you wanted folks to understand that you think is hard to appreciate or see from the outside?

Andrew Cheng: It's very difficult to produce drugs at the high standards required by the FDA when you don't have the resources that other individuals in the field have.

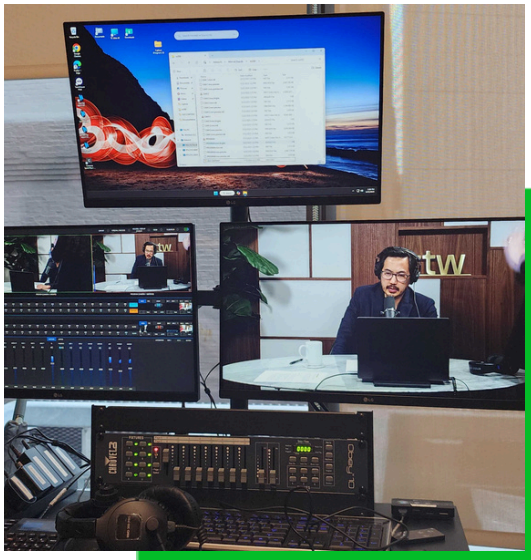
As a CEO of a biotech company, it's always challenging to raise capital and to have that be the number one issue: “Can we afford going to the next step?” Because in the end, the FDA doesn't look at biotech data.

There's no grading on the curve, as it were, that everyone is expected to adhere to the high standards, whether you're a large pharmaceutical company with seemingly endless capital, or you're a struggling biotech like Akero was for many, many years, that has to go to investors at every stage to raise the capital to go onto the next study.

Our results allowed us to go back to the investors and ask if they would continue to support us. And so, in a way, we had multiple market checks to make sure that the investors were willing to continue to choose us given the fact that there are roughly 800 biotech companies, all of whom are really searching for that investor capital.

Rod Wong: Yeah. It is not easy doing what you do. Thank you for joining us today. We really appreciate it.

Andrew Cheng: Happy to be here. Thanks again.



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