FLASH NOTE

Company Update

USA | Healthcare | Biotechnology

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Jefferies

Dicerna Pharmaceuticals (DRNA)

A Major Win on Regulatory Endpoints for DCR-PH1

BUY
Price target $48.00
Price $18.84

EQUITY RESEARCH AMERICAS

Key Takeaway

We spoke to six experts at the International Primary Hyperoxaluria (PH) Workshop in Chicago. We learned that the FDA is likely to accept a >50% reduction in urinary oxalate as a surrogate endpoint for DCR-PH1 approval. This is a major positive for DRNA as endpoints such as kidney stone reduction or renal function would involve higher risk and long followup. Separately, we learned that ALNY has a very early stage preclinical PH1 program.

Urinary Oxalate Endpoint For Trials Is A Major Positive for DCR-PH1. In our discussions with an expert at the PH conference, we learned that the primary endpoint for the DCR-PH1 clinical trial program will likely be reduction in urinary oxalate with a responder defined as a >50% reduction. Further, this expert indicated that, in discussions with the FDA and EMA, regulatory authorities have agreed that a drug for PH should be approvable with this biomarker endpoint. This is a major win both from a timeline and risk standpoint for DCR-PH1, as clinical endpoints like reduction in kidney stones and/or glomerular filtration rate are variable and would require large trials and long follow-up. The 50% bar is higher than prior trials for pyridoxine and for the current trials for Oxthera's Oxabact, both of which used a 30% reduction as a responder cutoff. The ongoing Oxthera trial is expected to have data in December with a week 8 endpoint. The expert indicated the FDA/EMA would still require long-term follow-up from these trials in order to prove that the reduction in urinary oxalate leads to better outcomes, but this follow-up would not be necessary for approval. DRNA has guided to a Phase 1 trial initiation in 2015 with proof-of-concept results by 2H15.

PH1 Is Heterogeneous, But 50% Reduction Is Probably Meaningful. In our conversations with six thought leaders, there was no real consensus as to how large a reduction in urinary oxalate would be meaningful. There is a fairly wide spectrum of PH1 severity due to variation in level of normal enzyme activity. Further, there is variability in patient kidney function that can further skew severity of symptoms, and fluctuations based on time of day and diet. However, experts highlighted that certain patients that received pyridoxine in clinical trials showed 70%+ reductions in oxalate and became asymptomatic. Thus, investigators were confident that the 50% reduction in oxalate could also show a reduction in symptoms.

We Learned ALNY Also Pursuing PH1. One investigator at the conference reported early results in two mice using ALNY-provided siRNAs against both glycolate oxidase (GO) and hydroxyproline oxidase (HPOX). This is the first we have heard of ALNY pursuing PH1. Much like DRNA's mouse results, the ALNY siRNAs were able to nearly completely knock down GO. However, while the DRNA mouse model saw urinary oxalate excretion reduced by up to 75%, the two PH1-simulating mice with ALNY's siRNA only saw a reduction of urinary oxalate of 27%. While there was discussion of potential compensatory mechanisms, we believe the small effect on urinary oxalate could be due the small sample size, or the use of a different PH1 mouse model. The ALNY program appears to be behind DRNA, although ALNY has not revealed any details of this program or its development strategy in PH1.

Knockout Of Upstream Enzyme Appears To Increase Efficacy, But May Be Unnecessary. ALNY has also developed siRNA to target hydroxyproline, a precursor to oxalate. Efficiency of this siRNA was worse than with GO, with only 50% knockdown. However, this knockdown was sufficient to reduce urinary oxalate by roughly the same amount as GO knockdown alone (~25%) When both the GO and HPOX siRNA were administered, the result was additive: a roughly 50% reduction in urinary oxalate. We view the double knockout as potentially unnecessary, especially if DRNA can replicate the ~75% preclinical reduction in urinary oxalate result in humans.

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Company Description

Dicerna Pharmaceuticals is a Watertown, MA-based therapeutics company focused on developing RNA interference (RNAi) technologies targeting liver and cancer. Dicerna has partnered two oncology development programs with the global pharmaceutical company Kyowa Hakko Kirin Co., Ltd. (KHK) targeting KRAS and CKAP5. DRNA's unpartnered programs are DCR-PH1 for Type 1 primary hyperoxaluria, a rare orphan disease resulting in renal failure, and DCR-M1711 targeting MYC for solid tumors.

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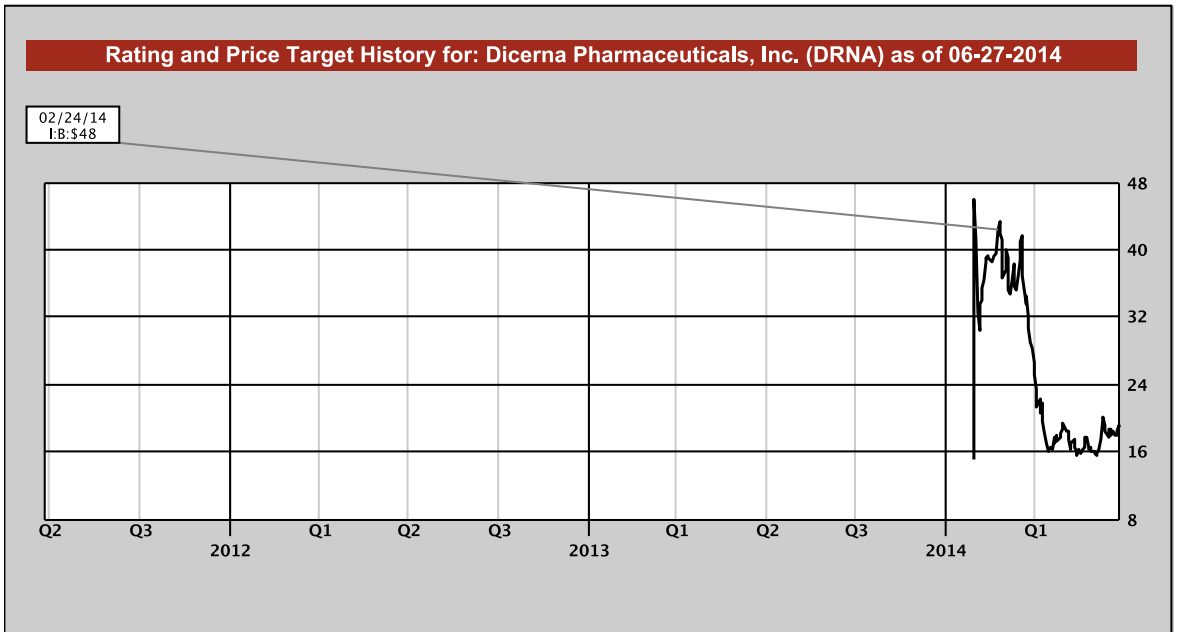
Other Companies Mentioned in This Report

- Dicerna Pharmaceuticals, Inc. (DRNA: $18.84, BUY)



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