Closer Look

MEMORANDUM

NuSirt announces phase 2 results for leucine/metformin combination in type 2 diabetes; Interview with management on plans in NAFLD/NASH - February 25, 2016

Executive Highlights

- NuSirt Biopharma recently announced phase 2 results for its leucine/low-dose metformin combination (NS-0100) in type 2 diabetes showing comparable glycemic improvements and greater improvements in liver enzymes vs. full-dose metformin alone.
- In a conversation with us, management shared updates on NuSirt's plans for its phase 2 leucine/ metformin/sildenafil combination in NAFLD/NASH, which is the company's top priority.

NuSirt Biopharma recently announced phase 2 results for its leucine/low-dose metformin combination (NS-0100) in type 2 diabetes showing comparable glycemic improvements and greater improvements in liver enzymes vs. full-dose metformin alone. These results met NuSirt's previously stated goal of demonstrating equivalent glucose-lowering efficacy with a lower dose of metformin, which could make the drug more tolerable for the approximately 20% of patients who experience serious GI side effects with standard doses. However, since the combination was not able to demonstrate superiority vs. full-dose metformin, NuSirt appears to have concluded that continuing the type 2 diabetes program would not be worth the investment at this point - yet another illustration of how high the bar has risen for new type 2 diabetes drugs. In a conversation with us, NuSirt management emphasized that the company is still interested in type 2 diabetes and suggested that these results support the potential of NuSirt's leucine/ metformin/sildenafil combination (NS-0200) to improve multiple metabolic abnormalities in people with type 2 diabetes and NAFLD/NASH.

Advancing the NAFLD/NASH program is clearly NuSirt's highest priority at the moment, a reflection of the great unmet need and significant opportunity in this area. The company initiated a phase 2a trial in November evaluating two doses of the combination vs. placebo in patients with NAFLD after a successful Series C financing round. The trial has a primary endpoint of change in hepatic fat after 16 weeks and is expected to complete in September 2016. NuSirt announced in December that the product had received an FDA Fast Track designation, which will allow for more frequent communication with the FDA and potentially an accelerated review timeline. Management suggested that phase 3 could begin in early 2017 if the phase 2 results are positive, and NuSirt should also be able to file under the abbreviated 505(b)(2) pathway. NuSirt is considering potential partnership options as part of its strategy for the product. The competitive landscape for NAFLD/NASH is quite crowded, which is understandable given the disease's growing prevalence and the lack of any approved treatments. NuSirt management suggested that NS-0200 may be able to differentiate itself as the best option for earlier stages of the disease, as it addresses multiple aspects of the disease and combines agents with well-understood safety profiles.

- **The phase 2a program in type 2 diabetes aimed to evaluate the glucose-lowering efficacy of the leucine/metformin combination (NS-0100) vs. metformin alone.** The first double-blind trial (n=102) randomized patients to one of three doses of the combination (125 mg, 250 mg, or 500 mg of metformin twice daily, all with 1,100 mg leucine) or metformin monotherapy (up to 850 mg twice daily) for four weeks. The primary endpoint was change in fasting plasma glucose; secondary endpoints included GI side effects and change in lipids and other glycemic parameters. A double-blind eight-week extension study (n=60) was primarily intended to evaluate change in A1c after three months. Full results will be presented as a poster at ADA in June.

In our conversation, NuSirt management emphasized that the combination led to dose-dependent, clinically meaningful reductions in glucose but acknowledged that the hope (from animal studies) of demonstrating superiority was not borne out.

- **The ongoing phase 2a trial in NAFLD/NASH is evaluating the effects of NS-0200 vs. placebo on liver fat.** The double-blind trial aims to enroll 100 patients who will be randomized to one of two doses of the combination (0.5 mg or 1.0 mg sildenafil twice daily, both with 500 mg metformin and 550 mg leucine) or placebo for 16 weeks. The primary endpoint is change in hepatic fat as assessed by MRI with proton density fat fraction (PDFF). NuSirt explained that the FDA will likely require a liver biopsy to assess fat content in pivotal trials but that the company felt this was too risky for a first-in-human study; the PDFF algorithm is well regarded in the field as an indicator of liver fat percentage. Secondary endpoints include changes in liver enzymes, A1c, fasting glucose, insulin, and lipids as well as adverse event rates. NuSirt management predicted that there would be a number of patients with diabetes in the trial, though people currently on metformin will be excluded.
- **NuSirt should be able to follow a fairly expedited development pathway for NS-0200.** Thanks to the Fast Track designation, NuSirt would be able to quickly begin discussions with the FDA once the phase 2 trial completes and hopefully initiate phase 3 in early 2017. The company believes that it will be able to file under the 505(b)(2) pathway, meaning it can rely on previous safety data for metformin and sildenafil rather than submitting a full new NDA. We have long thought that NuSirt's strategy of combining already approved drugs was a smart approach that should allow for a much smoother regulatory path.
- **We expect that NuSirt will likely seek a partner before beginning phase 3.** Management expressed openness to a future partnership during the interview but did not commit to any specific plans. NuSirt has been quite successful funding its trials to this point through venture capital financing, but having an experienced, well-resourced partner could be helpful in designing future trials and navigating regulatory and reimbursement issues.
- **NuSirt believes that NS-0200 may be able to differentiate itself as the preferred therapy earlier in the course of fatty liver disease.** Management noted that the drug addresses all three core conditions present in NASH - increased liver fat, inflammation, and fibrosis - whereas many other candidates in development only address one or two. Because of this and the fact that all three components have well-understood safety profiles, NuSirt believes the combination may be more appealing for patients with less advanced disease. See below for an overview of some of the other candidates in development for NAFLD/NASH.

Table 1: NAFLD/NASH Competitive Landscape

Sponsor	Drug Name	Class	Status	Other Remarks
Zydus Cadila	saroglitazar	dual PPAR alpha/ gamma agonist	Phase 3	Phase 3 trial initiated January 2015
Genfit	Elafibranor (GFT505)	dual PPAR alpha/ gamma agonst	Phase 3	Phase 2a results reported March 2015
Intercept Pharmaceuticals	Obeticholic acid	FXR agonist	Phase 3	Phase 3 trial recruiting; Completion expected October 2021

Immuron	IMM-124E	Oral immunotherapy that targets gut bacteria	Phase 2	Phase 2 trial recruiting; Completion expected February 2017
Galectin Therapeutics	GR-MD-02	Polysaccharide polymer that targets extracellular galectins	Phase 2 for fibrosis	Phase 2 trials in NASH cirrhosis and advanced fibrosis recruiting; Completion expected February 2018 and September 2016
Galmed Pharmaceuticals	Aramchol	Fatty-Acid/Bile-Acid Conjugate	Phase 2b	Phase 2 trial recruiting; Completion expected June 2017
NuSirt Biopharma	NS0200	leucine/PDE5 inhibitor/ metformin	Phase 2a	Phase 2a trial expected to complete in August 2016, according to ClinicalTrials.gov
Gilead	GS-4997	ASK-1 inhibitor	Phase 2	*Trial completion expected September 2016 according to* ClincalTrials.gov
NGM Biopharmaceuticals	NGM282	FGF19 agonist	Phase 2	See description on their website
Novo Nordisk	semaglutide	GLP-1 agonists	Phase 2	Plans to initiate a phase 2 trial in 2H16
Islet Sciences/BHV Pharma	Remogliflozin etabonate	SGLT-2 inhibitor	Phase 2	Investigated for both NASH and type 2 diabetes
Tobira Therapeutics	Cenicriviroc (CVC)	CCR2/CCR5 inhibitor	Phase 2	Phase 2 trial ongoing; Completion expected October 2017

Conatus Pharmaceuticals	IDN-6556	Caspase protease inhibitor	Phase 2	Phase 2 trial completed March 2015
Isis	ISIS-DGAT2Rx	DGAT-2 Inhibitor	Phase 1	Phase 1 trial initiated in September 2015.
AstraZeneca/Regulus Therapeutics	AZD4076/ RG-125	anti-microRNA (specifically anti-miR103/107 oligonucleotide)	Phase 1	Phase 1 trial initiated 4Q15
Nimbus Therapeutics	NDI-010976	Acetyl-CoA Carboxylase inhibitor	Phase 1	Phase 1 trial nearly complete according to website; Granted FDA Fast Track designation
Shire	SHP626	Apical sodium bile acid cotransporter inhibitor	Phase 1	Phase 1 trial completed July 2015
Enanta	Undisclosed	Undisclosed	Preclinical	Phase 1 to begin 2016
Metacrine	Undisclosed	Targets nuclear hormone receptors	Preclinical	Series A round in August 2015
Merck/NGM Biopharmaceuticals	NGM386	Targets NP201 pathway	Preclinical	Partnership agreement in February 2015
Merck/NGM Biopharmaceuticals	NGM395	Targets NP201 pathway	Preclinical	Partnership agreement in February 2015
NGM Biopharmaceuticals (Merck option)	NGM313	KLB-FGFR1c receptor complex agonist	Preclinical	Product page
Zafgen	ZGN-839	Oral MetAP2 inhibitor	Preclinical	IND filing expected 4Q15
Boehringer Ingelheim	Undisclosed	Undisclosed	Preclinical	Fibrotic processes in NASH listed as area of interest in discovery research

-- by Emily Regier and Kelly Close