MEMORANDUM

Isis reports positive topline phase 2 results for insulin sensitizer ISIS-PTP1BRx - February 9, 2015

Executive Highlights

- Isis reported positive topline results from a phase 2 trial of its novel insulin sensitizer ISIS-PTP1BRx showing significantly greater mean A1c reductions (0.7% vs. 0.2%; p = 0.03; baseline = 8.6%) and weight loss (p = 0.01; magnitude not disclosed) vs. placebo at 36 weeks.
- Full results will be presented at a medical meeting later this year. Isis plans to seek a partner before initiating phase 3 trials.

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Isis plans to seek a partner for ISIS-PTPBRx before initiating phase 3 trials, and we are very curious to gauge the level of interest from industry. On the one hand, companies might be hesitant to invest in an injectable therapy that does not appear to offer a significant efficacy advantage over existing injectable medications, at least based on the magnitude of the A1c reductions in this trial. On the other hand, the product's insulin-sensitizing mechanism of action (it inhibits PTP1B, a negative regulator of insulin action) offers considerable cause for excitement, as it would address the underlying pathophysiology of the disease to a greater extent than most existing drug classes. Isis has expressed hope that ISIS-PTP1BRx could help "refresh" the insulin sensitizer class, which has acquired a negative reputation in recent years due to the safety concerns associated with TZDs. We also believe the product's unique mechanism could make it very amenable to combination therapy with other classes like GLP-1 agonists - we would love to see Isis or a future partner explore this possibility.

- **Other companies developing PTP1B inhibitors include TransTech Pharma (TTP814; phase 2) and OHR Pharmaceutical (trodusquemine; phase 1).** Other companies developing novel insulin sensitizers include J&J (JNJ-41443532; phase 2), Metabolic Solutions (MSDC-0160 and MSDC-0602; phase 2), Shionogi (S-707106; phase 2), and XOMA (XMetS; preclinical).

Disappointingly, DiaMedica recently announced topline phase 2 results showing no significant improvements in glycemic control with its insulin sensitizer DM199.

-- by Emily Regier, Manu Venkat, and Kelly Close