CLOSER LOOK

MEMORANDUM

Lilly Ultra Rapid Lispro (URLi) phase 3 studies in T1D and T2D meet primary endpoint of non-inferior A1c reduction; Full readout and regulatory filings in 2019 - October 3, 2018

In breaking news from Lilly, two phase 3 studies of Ultra Rapid Lispro (URLi; LY900014) - PRONTO-T1D (n=1,222) and PRONTO-T2D (n=673) - met their primary efficacy endpoints of non-inferior A1c reduction at 26 weeks, compared to Lilly's Humalog (insulin lispro). No numbers were released, and Lilly aims to present these results in full and file with regulatory agencies sometime in 2019.

In addition to non-inferiority on A1c, both studies also demonstrated superiority to Humalog on both 1-hour and 2-hour postprandial glucose. To boot, the studies showed no difference in self-reported severe, nocturnal, or overall hypoglycemia - this is a good sign, though the dream with faster-acting insulin would actually be a *decrease* in hypoglycemia.

The reductions in postprandial excursions vs. Humalog serve as confirmation of smaller phase 1b studies that were presented in poster form at this year's ADA, as well as phase 2 data in type 1 and type 2 at ADA 2017. We'll be listening closely for any URLi commentary at EASD 2018, and very much look forward to release of more data soon.

Highlights: Interview with Mr. Tom Hardy, Senior Medical Director at Lilly

- **Lilly has not announced whether or not URLi offered an A1c-lowering benefit vs. Humalog; this data is forthcoming.** It is unclear whether Lilly purposefully chose to withhold this data for the time being, or if it isn't yet available.
- **CGM/time-in-range data were collected in a sub-study of PRONTO-T1D,** which included almost 300 participants. Results are not yet available internally, but we were encouraged to hear Mr. Hardy speak to the value these could offer on outcomes beyond A1c.
- **URLi is currently under investigation in a PK/PD study with comparators of Fiasp, NovoLog, and Humalog.** We were unable to find this trial on CT.gov. Pharmacokinetics, absorption, and PPG are points of interest.
- **Lilly intends to pursue approval for use in pumps in the US.** The PRONTO-Pump (n=48) phase 3 study completed in September 2018 and results are forthcoming; this was a safety and compatibility study requested by FDA, and everyone in this study used unblinded CGM. Lilly will now conduct a larger safety and efficacy study in pumps to support pump use and labeling in the US.
- **Lilly also intends to pursue a post-meal doing recommendation**. PRONTO-T1D included an open-label arm with recommendation to dose 20 minutes after the start of a meal. Mr. Hardy emphasized this doesn't mean Lilly would recommend routine use of post-meal dosing.
- **When we asked Mr. Hardy about the criticism some have leveraged against this generation (including Fiasp) of ultra-rapid acting insulins** - that they don't offer *enough* benefit - he offered some interesting context. As he tells it, when rapid acting insulin analogs came out, many had similar critiques: Some studies didn't show A1c benefit, and many didn't show hypoglycemia benefit. Many challenged whether rapid-acting analogs were worth it, even in type 1 diabetes. Today, this seems strange. Even if the situation isn't exactly analogous, he feels it can be difficult to demonstrate benefit in the treat-to-target trials currently used. As other outcomes become more important, ultra-rapid acting insulins may come to be seen in a different light.

Close Concerns' Questions

Did URLi demonstrate superiority on A1c-lowering vs. Humalog?

Will Lilly price URLi at parity with Humalog, as Novo Nordisk has done with Fiasp and NovoLog?

Will CGM data indicate a time-in-range benefit with URLi vs. Humalog?

What will head-to-head data with Novo Nordisk's Fiasp show?

How will patients, providers, and - perhaps most importantly - payers view URLi? Will this product help define the "ultra-rapid acting" class?

Will the entry of another ultra-rapid acting insulin make both Fiasp and URLi more accessible and affordable, or intensify pricing pressure?

-- by Sarah Kolk, Ann Carracher, Brian Levine, and Kelly Close