❮CLOSER LOOK

We're LIVE in Lisbon, listening to EXSCEL CVOT results on AZ's Bydureon (exenatide once-weekly). You could sense people shifting forward in their seats as Dr. Bernard Zinman announced data on the primary endpoint of three-point MACE - a hazard ratio of 0.91 (95% CI: 0.83-1.00). Talk about the "edge" of superiority with that upper bound of 1.00, but alas, as we learned from AZ's topline announcement in May, Bydureon demonstrated CV non-inferiority vs. placebo (p<0.001) and technically missed the statistical threshold for superiority (p=0.06) though the trend certainly looked positive; notably, there was superiority for those over 65 (presumably this is associated with longer duration of disease).

The question now is what distinguishes EXSCEL from positive CVOTs for other GLP-1 agonists, namely LEADER (Novo Nordisk's Victoza, liraglutide) and SUSTAIN 6 (semaglutide) - how much does trial design play a part? And/or, what distinguishes exenatide from liraglutide and semaglutide - what role do molecular differences play in these different CV outcomes? We've heard commentary from both sides at this meeting. Dr. Zinman praised EXSCEL for its "pragmatic" trial design more reflective of the real-world patient population: substantial primary prevention cohort, no run-in period (which in other studies, is used to exclude patients with low medication adherence), and wide range of concomitant medications allowed (including DPP-4s and SGLT-2s). On the other hand, Dr. Daniel Drucker highlighted differences between exendin-4-based GLP-1 agonists (exenatide and Sanofi's lixisenatide) vs. human GLP-1-based agents (liraglutide and semaglutide). We expect the contention to continue in the weeks and months ahead, but hopefully this will lead to strides forward in our understanding of the advanced GLP-1 class. EXSCEL, in our view, supports the overall advantages to this drug class, with compelling CV safety findings and a trend in the right direction on three-point MACE and CV death.

The EXSCEL paper was also just published in NEJM. We'll be back with a detailed look at all the data, plus full coverage of this brilliant symposium still going on : >. While not a showing of CV efficacy as we might've hoped to see, there is no shortage of learning to be gleaned from this CVOT - we'll keep our ear to the ground and keep sharing the insights we gather.

-- by Payal Marathe and Kelly Close