

Boehringer Ingelheim (BI) Response to 12-month Follow-Up of Tirzepatide for Type 2 Diabetes Evidence Report – March 31, 2023

Primary contact: Bonnie MK Donato, PhD (Bonnie.Donato@boehringer-ingelheim.com)

Boehringer Ingelheim (BI) appreciates the opportunity to respond to the request of submitting new evidence regarding Jardiance[®], since the January 2022 Evidence Report for Tirzepatide, for Type 2 Diabetes.

Summarizing the previous 12 months, we want to highlight that in 2022 FDA approved a new indication for Jardiance[®] to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure. Additionally, the FDA accepted 2 sNDAs for Jardiance[®]. Please see below for further details.

- *HFpEF FDA Approval (February 2022):*
 - On February 24th, the U.S. Food and Drug Administration (FDA) approved a new indication for Jardiance[®] (empagliflozin) 10 mg to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure.
 - The approval is based on findings from the EMPEROR-Preserved[®] phase III trial, in which Jardiance[®] demonstrated a 21% relative risk reduction (hazard ratio [HR]: 0.79; 95% confidence interval (CI): 0.69-0.90; absolute risk reduction [ARR]: 3.3%) compared with placebo for the composite primary endpoint of cardiovascular death or hospitalization for heart failure in adults with heart failure with left ventricular ejection fraction (LVEF) >40%.¹
- *CKD FDA sNDA Acceptance (January 2023):*
 - On January 20th, Boehringer Ingelheim and Lilly announced that the U.S. FDA accepted a supplemental New Drug Application (sNDA) for Jardiance[®] (empagliflozin) tablets, which is being investigated as a potential treatment to reduce the risk of kidney disease progression and cardiovascular death in adults with chronic kidney disease (CKD).
 - The sNDA is based on results from the landmark EMPA-KIDNEY phase III trial, in which Jardiance[®] significantly reduced the relative risk of kidney disease progression or cardiovascular death in adults with CKD by 28% (HR: 0.72; 95% CI: 0.64-0.82; ARR: 3.8%) compared with placebo, both on top of standard of care.²
- *FDA sNDA Acceptance for Children 10 Years of Age and Older with T2D (March 2023):*
 - On March 8th, Boehringer Ingelheim and Lilly announced that the U.S. FDA accepted an sNDA for Jardiance[®] (empagliflozin) tablets, investigating a potential new indication to lower blood sugar along with diet and exercise in children who are 10 years of age and older with type 2 diabetes.
 - The sNDA is based on the results from the DINAMO (DIabetes study of liNAGliptin and eMpagliflozin in children and adOlescents) trial, in which Jardiance[®] was associated with a statistically significant reduction in the primary endpoint of change from baseline in A1c (a marker of average blood sugar) at 26 weeks compared with placebo for participants aged 10-17 years with type 2 diabetes.³

If you have any questions or would like further information, please let us know.

References

1. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med.* 2021;385(16):1451-1461. doi:10.1056/NEJMoa2107038
2. The EMPA-KIDNEY Collaborative Group, Herrington WG, Staplin N, et al. Empagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med.* 2023;388(2):117-127. doi:10.1056/NEJMoa2204233
3. Pediatric: Laffel LM, Danne T, Klingensmith GJ, et al. Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO): a multicentre, randomised, double-blind, parallel group, phase 3 trial. *Lancet Diabetes Endocrinol.* 2023;11(3):169-181. doi:10.1016/S2213-8587(22)00387-4



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Eli Lilly and Company

VIA ELECTRONIC DELIVERY

Lilly Corporate Center
Indianapolis, Indiana 46285
U.S.A.
+1.317.276.2000
www.lilly.com

Steven D. Pearson, MD, MSc
Institute for Clinical and Economic Review (ICER)
14 Beacon Street, Suite 800
Boston, MA 02108

Re: ICER's Assessment of Tirzepatide for Type 2 Diabetes: 12-Month Check-Up

Dr. Pearson,

Eli Lilly and Company (Lilly) appreciates the opportunity to provide input during ICER's 12-month review of its Final Evidence Report assessing tirzepatide for the treatment of type 2 diabetes (T2DM).

As part of its review, Lilly respectfully requests that ICER consider the following in its 12-month check-up:

1. On May 13, 2022, the U.S. Food and Drug Administration (FDA) approved Mounjaro[®] (tirzepatide) as a first-in-class glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. In its announcement, FDA noted that: "Mounjaro was effective at improving blood sugar and was more effective than the other diabetes therapies with which it was compared in clinical studies."¹
2. On Dec. 12, 2022, the American Diabetes Association (ADA) published its 2023 Standards of Care in Diabetes (Standards). The updated Standards now include tirzepatide as a glucose-lowering option with the potential for weight loss.² Additionally, the Standards' updated evidence-based guidelines more explicitly address weight management as an impactful component of T2DM management and note that treatment regimens should consider approaches that support weight management.³
3. Since the release of ICER's Final Evidence Report on Feb. 15, 2022, a number of publications and presentations have addressed tirzepatide as a treatment option for T2DM. Lilly has included applicable literature from the post-assessment period in Appendix A.

Lilly is excited about forthcoming data from ongoing studies to further support the clinical effectiveness and value of Mounjaro[®] (tirzepatide) for the treatment of T2DM. We look forward to sharing results from SURPASS-AP-Combo⁴, SURPASS-6, SURMOUNT-2, and SURPASS-CVOT as they become available.

Sincerely,

Christian Nguyen, PharmD, MBA, MS
Senior Vice President, Value, Evidence & Outcomes
Eli Lilly and Company
nguyen_christian_t@lilly.com

¹ U.S. Food and Drug Administration. (2022, May 13). FDA Approves Novel, Dual-Targeted Treatment for Type 2 Diabetes [New Release]. <https://www.fda.gov/news-events/press-announcements/fda-approves-novel-dual-targeted-treatment-type-2-diabetes>

² ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, Collins BS, Cusi K, Das SR, Gibbons CH, Giurini JM, Hilliard ME, Isaacs D, Johnson EL, Kahan S, Khunti K, Kosiborod M, Leon J, Lyons SK, Murdock L, Perry ML, Prahalad P, Pratley RE, Seley JJ, Stanton RC, Sun JK, Woodward CC, Young-Hyman D, Gabbay RA, on behalf of the American Diabetes Association. Summary of Revisions: Standards of Care in Diabetes-2023. *Diabetes Care*. 2023 Jan 1;46(Suppl 1):S5-S9. doi: 10.2337/dc23-Srev. PMID: 36507641; PMCID: PMC9810459.

³ Nuha A. ElSayed, Grazia Aleppo, Vanita R. Aroda, Raveendhara R. Bannuru, Florence M. Brown, Dennis Bruemmer, Billy S. Collins, Marisa E. Hilliard, Diana Isaacs, Eric L. Johnson, Scott Kahan, Kamlesh Khunti, Jose Leon, Sarah K. Lyons, Mary Lou Perry, Priya Prahalad, Richard E. Pratley, Jane Jeffrie Seley, Robert C. Stanton, Robert A. Gabbay; on behalf of the American Diabetes Association, 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023. *Diabetes Care* 1 January 2023; 46 (Supplement_1): S140–S157. <https://doi.org/10.2337/dc23-S009>.

⁴ Summary results information from SURPASS-AP-Combo posted to ClinicalTrials.gov on January 6, 2023; published results forthcoming.

Appendix A – Literature for Review

1. Sattar, N., McGuire, D.K., Pavo, I. et al. Tirzepatide cardiovascular event risk assessment: a pre-specified meta-analysis. *Nat Med* 28, 591–598 (2022). <https://doi.org/10.1038/s41591-022-01707-4>.
2. Valentine WJ, Hoog M, Mody R, et al. Long-term cost-effectiveness analysis of tirzepatide versus semaglutide 1.0 mg for the management of type 2 diabetes in the United States. *Diabetes Obes Metab*. 2023;1-9. doi:10.1111/dom.14979.
3. Vadher K, Patel H, Mody R, et al. Efficacy of tirzepatide 5, 10 and 15 mg versus semaglutide 2 mg in patients with type 2 diabetes: An adjusted indirect treatment comparison. *Diabetes Obes Metab*. 2022;24(9): 1861-1868. doi:10.1111/dom.14775.
4. Heerspink HJL, Sattar N, Pavo I, et al. Effects of tirzepatide versus insulin glargine on kidney outcomes in type 2 diabetes in the SURPASS-4 trial: post-hoc analysis of an open-label, randomised, phase 3 trial. *Lancet Diabetes Endocrinol*. 2022 Nov;10(11):774-785. doi: 10.1016/S2213-8587(22)00243-1.
5. Pirro V, Roth KD, Lin Y, et al. Effects of Tirzepatide, a Dual GIP and GLP-1 RA, on Lipid and Metabolite Profiles in Subjects With Type 2 Diabetes. *J Clin Endocrinol Metab*. 2022 Jan 18;107(2):363-378. doi: 10.1210/clinem/dgab722.
6. Dahl D, Onishi Y, Norwood P, et al. Effect of Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control in Patients With Type 2 Diabetes: The SURPASS-5 Randomized Clinical Trial. *JAMA*. 2022 Feb 8;327(6):534-545. doi: 10.1001/jama.2022.0078.
7. Lingvay, I, Cheng, AY, Levine, JA, et al. Achievement of glycaemic targets with weight loss and without hypoglycaemia in type 2 diabetes with the once-weekly glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist tirzepatide: A post hoc analysis of the SURPASS-1 to -5 studies. *Diabetes Obes Metab*. 2023; 25(4): 965- 974. doi:10.1111/dom.14943.
8. Matza L, Stewart K, Fernández Landó L, Patel H, Boye K. “Qualitative Exit Interviews Examining the Patient Experience in Clinical Trials of Tirzepatide for Treatment of Type 2 Diabetes.” *The Patient: Patient-Centered Outcome*. 2022;15, 367–377.
9. Thieu V, Boye K, Lee C, Sapin H. “Decreased HbA1c Levels Associated with Improved Patient Reported Outcomes in T2D Patients Treated with Tirzepatide.” Poster at the International Diabetes Federation Conferences, Lisbon, Portugal; December 5-8, 2022.
10. Boye K, Thieu V, Lee C, and Sapin H. “Higher Weight Loss is Associated with Improved Patient Reported Outcomes in T2D Patients Treated with Tirzepatide.” Poster at the International Diabetes Federation Conferences, Lisbon, Portugal; December 5-8, 2022.