Comments on Appraisal consultation document Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes [ID756]

Order number *(For internal use only)*	**Section Number** Indicate **number** or **'general'** if your comment relates to the whole document	**Page Number** Indicate **number** or **'general'** if your comment relates to the whole document	**Comments** **Please insert each new comment in a new row.** **Please do not paste other tables into this table, as your comments could get lost – type directly into this table.**
1.	1	3	Boehringer Ingelheim agrees with the Appraisal Committee's preliminary recommendation as stated in section 1.1 and 1.2.
2.	4.3	8	Where stating "The reductions for empagliflozin were also greater than those for sitagliptin (statistical significance was not presented).": In the publication by Roden et al (2013), Figure 2 (changes in HbA_{1c} and FPG) details the differences and statistical significance values of the adjusted mean change from baseline in HbA_{1c} for empagliflozin 10 mg and 25 mg compared to sitagliptin. The difference in adjusted mean change from baseline in HbA_{1c} for empagliflozin 10 mg compared to sitagliptin is 0.00% (p= 0.96) and -0.12% (p= 0.106) for empagliflozin 25 mg compared to sitagliptin.
3.	4.4	9	Where stating "Compared with placebo, all SGLT-2 inhibitors reduced systolic blood pressure, however no results were statistically significant.": In the publication by Roden et al (2013), Figure 4 (Changes in blood pressure in the full analysis set) illustrates the adjusted mean change from baseline in systolic blood pressure (SBP) and associated p-values. The difference in adjusted mean change from baseline in SBP for empagliflozin 10 mg compared to placebo is -2.6 mmHg (p= 0.023) and -3.4 mmHg (p= 0.003) for empagliflozin 25 mg compared to placebo. Therefore, the results for empagliflozin 10 mg and 25 mg compared to placebo were statistically significant in reducing SBP.
4.	4.47	27	Where stating "The company did not present any sensitivity or scenario analyses for model B.": Boehringer Ingelheim provided 4 economic models (model A and model B, each carried out at 24 and 52 weeks). This was deemed extensive enough to capture any areas of uncertainty. As the two models validate each other in their direction of results it was not deemed necessary to present the sensitivity analysis. Nevertheless, one-way sensitivity analyses were carried out on both model A and model B, showing that the results are most sensitive to the incidence of hypoglycaemic events (empagliflozin 10mg and empagliflozin 25 mg and the comparator), likely due to the wide 95% confidence intervals. Weight loss and the incidence of UTIs also have a considerable impact on the ICER. Other variables, including cost and utility decrements associated with AEs had a comparably minimal impact on the ICER results.
5.	4.48	27	Where stating "The AG also stated that it was concerned about why the reported UKPDS costs of model B were around half of those of

			model A, whereas the QALY values of model A and B were similar. It stated that the reason for the discrepancy was unclear.”: It is known with the UKPDS Outcomes Model 1 (OM1) that running 40 years together (as was done for model A) versus running the model 1 year at a time (as was done for model B), results in the costs being underestimated for the latter. Usually, they are underestimated by about half. This has already been acknowledged as an issue by the Oxford team of developers. The reason model B was ran for 1 year at a time, was to be able to account for treatment switches and weight changes on a yearly basis, since these are not directly modelled for in the UKPDS model. This workaround method was validated with the developers, who have improved the issue in the newly developed UKPDS Outcomes Model 2 (OM2). Overall, the costs are underestimated for all treatment groups in model B compared to model A. Therefore, the resulting incremental cost-effectiveness ratios (ICERs) are still reflective of the relative differences between treatments for both models.
6.	4.65	38	Boehringer Ingelheim agrees with the Committee’s opinion that “weight loss does affect quality of life”. Boehringer Ingelheim also agrees that “the evidence [shows] that SGLT-2 inhibitors do have a significant effect on weight loss, and that the AG’s BMI-2 scenario (in which weight gains were maintained and weight losses rebounded to natural history after 1 year) best reflected the treatment effect on weight loss.” Nevertheless, it remains a valid point that the very small QALY differences between treatments make the ICERs unstable.
7.			