Error in presentation of change in lipid data in the NICE submission

In the canagliflozin NICE submission of 15th October 2013, the change in lipid levels over time were incorrectly described as being described as change in HDL-C and LDL-C in **mmol/L**. The data presented were instead the **percent change** in HDL-C and LDL-C over time.

Table 1. Tables and Figures in the canagliflozin submission incorrectly labelled as mmol/L that are in fact percent change in HDL-C and LDL-C over time

	Main submission	Appendices
Dual therapy	Figures 13 and 14	Appendix 6, Tables 19 and 20
Triple therapy	Figures 25, 26 and 27	Appendix 6, Tables 26, 27 and 28
Add-on to insulin	Figure 32	Appendix 6, Tables 33, 34 and 35.

For completeness, below is given the data as change in HDL-C and LDL-C in mmol/L.

Change in lipids - Dual therapy

The change in HDL-C and LDL-C reported in DIA3006 and DIA3009 trials were presented in Tables 19 to 21 of Appendix 6 and in Figure 13 and Figure 14 of the submission relate to the percent change in HDL-C and LDL-C between baseline and either the primary time point (for the tables) or the end of the trials (for the figures).

When considering the absolute change in HDL-C and LDL-C in mmol/L, the results are as follows:

- DIA3006: Canagliflozin 300mg and 100mg (in combination with metformin) resulted in an increase in both mean HDL-C and LDL-C.
    - At week 26, the mean change in HDL-C from baseline was 0.05mmol/L (95% CI: 0.028;0.065) for sitagliptin, 0.11mmol/L (95% CI: 0.085;0.130) for canagliflozin 100mg and 0.12mmol/L (95% CI: 0.101;0.147) for canagliflozin 300mg. The mean change in LDL-C from baseline was 0.02mmol/L (95% CI: -0.051;0.098) for sitagliptin 100mg, 0.11mmol/L (95% CI: 0.036;0.185) for canagliflozin 100mg, and 0.20mmol/L (95% CI: 0.123;0.284) for canagliflozin 300mg. (1)
    - At week 52, the mean change in HDL-C was 0.06mmol/L (95% CI: 0.038;0.075) for sitagliptin, 0.11mmol/L (95% CI: 0.091;0.130)for canagliflozin 100mg and 0.13mmol/L (95% CI: 0.108;0.160)for canagliflozin 300mg. The LS mean change for LDL-C (mmol/L) was 0.11mmol/L (95% CI: 0.034;0.184) for sitagliptin, and 0.16mmol/L (95% CI: 0.077;0.248) and 0.16mmol/L (95% CI: 0.077;0.243)for canagliflozin 100mg and 300mg, respectively. (2)
- DIA3009:
    - At week 52, canagliflozin 100mg and 300mg resulted in an increase in LS mean in HDL-C of 0.07mmol/L (95% CI: 0.056;0.093), 0.09mmol/L (95% CI: 0.070;0.106) respectively versus -0.01mmol/L (95% CI: -0.029;0.003) for glimepiride. The mean change in LDL-C from baseline was 0.13mmol/L (95% CI: 0.072;0.197) and 0.22mmol/L (95% CI: 0.151;0.289) for canagliflozin 100mg and 300mg respectively versus 0.04mmol/L (95% CI: -0.023;0.103) for glimepiride. (3)

- At week 104, the mean change in HDL-C from baseline was -0.01mmol/L (95% CI: -0.032;0.004) for glimepiride, 0.09mmol/L (95% CI: 0.067;0.106)for canagliflozin 100mg and 0.10mmol/L (95% CI: 0.079;0.118)for canagliflozin 300mg. The mean change in LDL-C from baseline was 0.05mmol/L (95% CI: -0.021;0.111) for glimepiride, 0.15mmol/L (95% CI: 0.088;0.220) for canagliflozin 100mg, and 0.20mmol/L (95% CI: 0.129;0.273)for canagliflozin 300mg. (4) These results demonstrated that change in lipid levels plateaued after 52 weeks indicating that the main effect of canagliflozin on lipids is observed within the first year of therapy. (4)

Change in lipid levels – Triple therapy

Similarly, the change in HDL-C and LDL-C reported in DIA3015, DIA3002 and DIA3012 trials and which were presented in Tables 26 to 28 of Appendix 6 and in Figure 25 to Figure 27 of the submission relate to the percent change in HDL-C and LDL-C between baseline and either the primary time point (for the tables) or the end of the trials (for the figures).

When considering the absolute change in HDL-C and LDL-C in mmol/L, the results are as follows:

DIA3015 (in combination with metformin and a SU)

- At *week 5*2, canagliflozin 300mg in combination with MET+SU resulted in an increase in HDL-C mmol/L of -0.08 (95% CI: 0.063;0.102) was observed in canagliflozin 300mg versus a change of and -0.00 (95% CI: -0.023;0.015) for sitagliptin 100mg. An increase in LDL-C mmol/L of 0.13mmol/L (95%CI: 0.049;0.217) versus an increase of 0.01mmol/L (95% CI: -0.056;0.082) for sitagliptin 100mg. (5;6)

DIA3002 (in combination with metformin and a SU)

- At week 26, canagliflozin 100mg and 300mg resulted in an increase in HDL-C of 0.06mmol/L (95% CI: 0.035;0.088) and 0.07mmol/L (95% CI: 0.044;0.097) respectively versus 0.02mmol/L 95% CI: (-0.011;0.050) for placebo and an increase in LDL-C of 0.01mmol/L (95% CI: -0.091;0.115) and 0.14mmol/L (95% CI: 0.032;0.255)respectively versus -0.00mmol/L (95% CI: -0.116;0.106) for placebo. (7)

- At week 52, canagliflozin 100mg and 300mg resulted in an increase in HDL-C (minus placebo) of 0.04mmol/L (95%CI: 0.005;0.085) and 0.06mmol/L (95%CI: -0.019;0.099), respectively, and an increase in LDL-C (minus placebo) of -0.14mmol/L (95%CI: -0.302;0.026) and 0.15mmol/L (95%CI: -0.017;0.311) respectively. (8)

In DIA3012 (in combination with metformin and a TZD)

- At week 26, canagliflozin 100mg and 300mg resulted in an increase in HDL-C of 0.08mmol/L (95% CI: 0.048;0.119) and 0.09mmol/L (95% CI: 0.052;0.126) respectively, versus 0.02mmol/L 95% CI: (-0.013;0.049) for placebo, and an increase in LDL-C of 0.11mmol/L (95% CI: -0.007;0.221) and 0.23mmol/L (95% CI: 0.104;0.365) versus -0.11mmol/L (95% CI: -0.254;0.035) for placebo. (9)

- At week 52, canagliflozin 100mg and 300mg resulted in an increase in HDL-C of 0.08mmol/L (95% CI: 0.036;0.125) and 0.14mmol/L (95% CI: 0.089;0.184)

respectively, and an increase in LDL-C of 0.08mmol/L (95% CI: -0.056;0.220) and 0.21mmol/L (95% CI: -0.001;0.424) respectively. (10)

Change in lipid levels – Add-on to Insulin

Similarly, the change in HDL-C and LDL-C reported in DIA3008 insulin sub-study were presented in Tables 33 to 35 of Appendix 6 and in Figure 32 of the submission relate to the percent change in HDL-C and LDL-C between baseline and 18 weeks.

When considering the absolute change in HDL-C and LDL-C in mmol/L, the results for DIA3008 insulin sub-study (in combination with insulin and standard of care) are as follows:

- At week 18, canagliflozin 100mg and 300mg resulted in an increase in HDL-C of 0.03mmol/L (95% CI: 0.011;0.042) and 0.07mmol/L (95% CI: 0.049;0.082) respectively versus 0.01mmol/L (95% CI: -0.004;0.028) for placebo and an increase in LDL-C of 0.04mmol/L (95% CI: -0.021;0.100) and 0.10mmol/L (95% CI: 0.043;0.160) respectively versus 0.01mmol/L (95% CI: -0.048;0.063) for placebo. (11)

Reference List

(1) Janssen Research & Development L. Clinical Study report - JNJ-28431754 DIA3006 (26-week double-blind extension phase) - The CANTATA-D Trial JNJ. 2012 Apr 20.

(2) Janssen Research & Development L. Clinical Study report - JNJ-28431754 DIA3006 (52-week Core double-blind period) - The CANTATA-D Trial JNJ. 2012 Dec 18.

(3) Janssen Research & Development L. Clinical Study Report - JNJ-28431754 DIA3009 (52-week Core Double-Blind Period) - The CANTATA-SU Trial JNJ. 2012 May 15.

(4) Janssen Research & Development L. Clinical Study report - JNJ-28431754 DIA3009 (104-week double-blind treatment phase) - CANTATA-SU Trial JNJ. 2013 Jul 24.

(5) Janssen Research & Development L. Clinical Study Report - JNJ-28431754 DIA3015 (52-week Double-blind period) - The CANTATA-D2 Trial JNJ. 2012 May 3.

(6) Schernthaner G, Gross JL, Rosenstock J, Guarisco M, Fu M, Yee J, et al. Canagliflozin Compared With Sitagliptin for Patients With Type 2 Diabetes Who Do Not Have Adequate Glycemic Control With Metformin Plus Sulfonylurea: A 52-week randomized trial. Diabetes Care 2013 Sep;36(9):2508-15.

(7) Janssen Research & Development L. Clinical Study Report - JNJ-28431754 DIA3002 (26-week core double-blind period) - CANTATA-MSU Trial JNJ. 2012 Apr 30.

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(9) Janssen Research & Development L. Clinical Study Report - JNJ-28431754 DIA3012 - 26-week Core Double-Blind period. 2012 Apr 5.

(10) Janssen Research & Development L. Clinical Study Report - JNJ-28431754 DIA3012 (52-week extension double-blind period) - CANTATA-MP Trial JNJ. 2013 May 23.

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