

# Apparent subadditivity of the efficacy of initial combination treatments for type 2 diabetes is largely explained by the impact of baseline HbA1c on efficacy

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**Aim:** To explain the subadditive efficacy typically observed with initial combination treatments for type 2 diabetes.

**Methods:** Individual subject data from 1186 patients with type 2 diabetes [mean glycated haemoglobin (HbA1c) = 8.8%] treated with metformin, canagliflozin or canagliflozin + metformin were used. The baseline HbA1c versus  $\Delta$ HbA1c relationships for monotherapy arms were determined using analysis of covariance and then used to predict efficacy in the combination arms by modelling how applying one treatment lowers the 'effective baseline HbA1c' for a second treatment. The model was further tested using data from several published combination studies.

**Results:** The mean  $\Delta$ HbA1c levels were  $-1.25$ ,  $-1.33$ ,  $-1.37$ ,  $-1.77$  and  $-1.81\%$  with metformin, canagliflozin 100 mg, canagliflozin 300 mg, canagliflozin 100 mg/metformin and canagliflozin 300 mg/metformin, respectively. Using the monotherapy results, the predicted efficacy for the canagliflozin/metformin arms was within 10% of the observed values using the new model, whereas assuming simple additivity overpredicted efficacy in the combination arms by nearly 50%. For 10 other published initial combination studies, predictions from the new model [mean (standard error) predicted  $\Delta$ HbA1c = 1.67% (0.14)] were much more consistent with observed values [ $\Delta$ HbA1c = 1.72% (0.12)] than predictions based on assuming additivity [predicted  $\Delta$ HbA1c = 2.19% (0.21)].

**Conclusions:** The less-than-additive efficacy commonly seen with initial combination treatments for type 2 diabetes can be largely explained by the impact of baseline HbA1c on the efficacy of individual treatments. Novel formulas have been developed for predicting the efficacy of combination treatments based on the efficacy of individual treatments and the baseline HbA1c of the target patients.

**Keywords:** canagliflozin, initial combination therapy, metformin, type 2 diabetes

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## Introduction

Clinicians typically recommend that patients with newly diagnosed type 2 diabetes initiate lifestyle changes, such as changes to diet and exercise, as the first step to improving glycaemic control; however, many patients eventually require pharmacological intervention [1]. Metformin is commonly the first-line treatment and, as the disease progresses, additional therapies are added to maintain glucose control [1]. Initial combination therapy with metformin and another antihyperglycaemic agent is increasingly being used to lower glycated haemoglobin (HbA1c) levels, especially in patients who would benefit from earlier and more aggressive glycaemic control [1]. Several fixed-dose combinations are available, including combinations of metformin and other agents [e.g. dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium glucose co-transporter 2 (SGLT2)

inhibitors and thiazolidinediones], as well as combinations of DPP-4 inhibitors with SGLT2 inhibitors or thiazolidinediones. Notably, the HbA1c lowering that is observed with fixed-dose combination therapies in type 2 diabetes is typically less than the sum of changes in the individual treatment arms [2–10]. While the subadditive efficacy commonly seen with combination treatments may be attributable, at least in part, to specific pharmacodynamic interactions between different treatment classes, the consistent subadditivity seen with multiple different combinations suggests that there may be additional explanations besides direct, detrimental pharmacodynamic interactions between different treatment classes.

In a randomized, double-blind, active-controlled study, the efficacy and safety of initial combination therapy with canagliflozin, an SGLT2 inhibitor, and metformin were evaluated in patients with type 2 diabetes who had inadequate glycaemic control with diet and exercise over 26 weeks (ClinicalTrials.gov Identifier: NCT01809327) [11]. The canagliflozin 100 mg + metformin and canagliflozin 300 mg + metformin combinations provided statistically significant reductions in HbA1c relative to metformin, canagliflozin 100 mg or canagliflozin 300 mg alone. Non-inferiority of HbA1c lowering was demonstrated with canagliflozin 100 and 300 mg versus

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metformin. As anticipated based on results that were observed with other fixed-dose combinations [2–10], the efficacy of the combination arms was less than the sum of the changes in efficacy that was obtained with the monotherapy components. Individual subject data from the present study were used to develop a conceptual and quantitative explanation for the subadditivity that is commonly observed in combination treatment studies. By using a modelling approach that makes the assumption that the steady-state efficacy of combination treatment should be the same as that which would be obtained if the two treatments were applied in sequence, with one of the treatments applied first and the second treatment added once steady-state is reached with the first treatment, a better estimate of the efficacy of combination treatment can be made. In this model, treatment with the first agent effectively lowers the baseline HbA1c level for the second treatment. Because the efficacy of each individual treatment depends on the baseline HbA1c, the efficacy of the combination is expected to be lower since the second treatment of the combination will act on patients at a lower baseline HbA1c than if the second treatment was applied initially as monotherapy.

The model developed in the present manuscript provides a quantitative method for predicting the efficacy of combination treatment with different agents, based on the efficacy of the individual agents, and shows that the efficacy of combination treatment is expected to be subadditive even when there are no direct pharmacodynamic interactions. The model is applied to data from the study of the canagliflozin + metformin combinations and several previously published combination treatment studies with other agents.

## Materials and Methods

### Canagliflozin + Metformin Study

Individual subject data from a combination treatment study with canagliflozin and metformin were used in developing the model. Details of the study design have been reported [11]. Briefly, this was a randomized, double-blind, active-controlled, parallel-group, five-arm, multicentre phase III study that enrolled patients with type 2 diabetes aged 18–75 years with inadequate glycaemic control ( $\text{HbA1c} \geq 7.5$  to  $\leq 12.0\%$ ) on diet and exercise at screening and who were not on an anti-hyperglycaemic agent for at least 12 weeks before screening. Eligible patients were randomized to metformin extended release alone, canagliflozin 100 mg, canagliflozin 300 mg, co-administration of canagliflozin 100 mg and metformin extended release, or co-administration of canagliflozin 300 mg and metformin extended release (1 : 1 : 1 : 1 : 1) for 26 weeks. The primary efficacy endpoint was change from baseline in HbA1c at week 26.

### Mathematical Modelling for the Relationship Between Baseline HbA1c and Treatment Effect

Analysis of covariance (ANCOVA) modelling was carried out using the data from all treatment arms to confirm that baseline HbA1c ( $\text{HbA1c}_{\text{BL}}$ ) was a significant covariate influencing  $\Delta\text{HbA1c}$ ; this was confirmed ( $p < 10^{-90}$  for effect of  $\text{HbA1c}_{\text{BL}}$ ).

Next, the effect of each treatment arm was modelled to be a linear function of  $\text{HbA1c}_{\text{BL}}$  using the equation

$$\Delta\text{HbA1c} = -m \cdot (\text{HbA1c}_{\text{BL}} - \text{HbA1c}_{\text{NoEL}}) \quad (1)$$

where  $\text{HbA1c}_{\text{NoEL}}$  is the value of baseline HbA1c at which no mean reduction in HbA1c would be observed (i.e. the x-intercept of the plot of  $\Delta\text{HbA1c}$  vs  $\text{HbA1c}_{\text{BL}}$ ) and  $m$  is a slope parameter describing the influence of  $\text{HbA1c}_{\text{BL}}$  on  $\Delta\text{HbA1c}$ . The linear relationship assumed in Equation 1 is expected to be a reasonable approximation of the actual relationships in typical studies in patients with type 2 diabetes who have  $\text{HbA1c}_{\text{BL}}$  values ranging from  $\sim 7$  to  $12\%$ ; however, because most antihyperglycaemic agents have virtually no effect on plasma glucose when subjects are normoglycaemic, Equation 1 should only be used when  $\text{HbA1c}_{\text{BL}} > \text{HbA1c}_{\text{NoEL}}$  (and  $\Delta\text{HbA1c}$  would be assumed to be 0 if  $\text{HbA1c}_{\text{BL}} \leq \text{HbA1c}_{\text{NoEL}}$ ).

The effect of combination treatments in the canagliflozin + metformin study were modelled two separate ways: (i) by directly fitting the data to combination treatment arms using Equation 1 and (ii) by predicting the combination response based on the individual monotherapy arms assuming no direct pharmacodynamic interactions between the two treatments (i.e. the  $m$  parameters for each of the individual treatments are not altered by the other treatment used in combination) and assuming that the combination efficacy is the same as that which would be observed if the treatments were applied in a sequence with one treatment applied first as monotherapy and the second treatment added when steady state is achieved with the first treatment. The latter is achieved by using Equation 1 to apply the effect of two individual treatment arms as monotherapy (labelled Rx1 and Rx2), as follows:

$$\Delta\text{HbA1c}_{\text{Rx1}} = -m_{\text{Rx1}} \times (\text{HbA1c}_{\text{BL}} - \text{HbA1c}_{\text{NoEL}}) \quad (2)$$

$$\Delta\text{HbA1c}_{\text{Rx2}} = -m_{\text{Rx2}} \times (\text{HbA1c}_{\text{BL}} - \text{HbA1c}_{\text{NoEL}}) \quad (3)$$

where  $-m_{\text{Rx1}}$  and  $-m_{\text{Rx2}}$  are the slopes of the best-fit lines to the individual treatment arms,  $\text{HbA1c}_{\text{BL}}$  is the baseline HbA1c value and  $\text{HbA1c}_{\text{NoEL}}$  is the x-intercept of the best-fit line. To predict the steady-state efficacy of combination treatment with Rx1 and Rx2 assuming no direct pharmacodynamic interactions between the treatments (i.e. treatment with one agent does not affect the  $m$  value for the other agent), it is assumed that the same steady-state efficacy would be obtained if the treatments were applied sequentially (i.e. Rx1 is applied first, and when a new steady-state HbA1c level is achieved, Rx2 is added on top of Rx1). Because the efficacy of each of the individual treatment arms depends on a patient's  $\text{HbA1c}_{\text{BL}}$ , this conceptual model of applying the treatments sequentially enables the effect of one treatment lowering the 'effective baseline HbA1c' for the other treatment to be quantified.

Applying Rx1 first (and giving a sufficient time for HbA1c to equilibrate at a new level) gives

$$\begin{aligned} \text{HbA1c}_{\text{after Rx1}} &= \text{HbA1c}_{\text{BL}} + \Delta\text{HbA1c}_{\text{Rx1}} = (1 - m_{\text{Rx1}}) \\ &\times \text{HbA1c}_{\text{BL}} + m_{\text{Rx1}} \times \text{HbA1c}_{\text{NoEL}} \end{aligned}$$

and applying Rx2 to a subject starting at this HbA1c level gives

$$\Delta\text{HbA1c}_{\text{Rx2 after Rx1}} = -m_{\text{Rx2}} \times (\text{HbA1c}_{\text{after Rx1}} - \text{HbA1c}_{\text{NoEL}})$$

$$= -(m_{\text{Rx2}} - m_{\text{Rx1}} \times m_{\text{Rx2}}) \times (\text{HbA1c}_{\text{BL}} - \text{HbA1c}_{\text{NoEL}})$$

so that the efficacy of the combined treatment is given by

$$\Delta\text{HbA1c}_{\text{Rx1+Rx2}} = \Delta\text{HbA1c}_{\text{Rx1}} + \Delta\text{HbA1c}_{\text{Rx2 after Rx1}}$$

$$= -(m_{\text{Rx1}} + m_{\text{Rx2}} - m_{\text{Rx1}} \times m_{\text{Rx2}})$$

$$\times (\text{HbA1c}_{\text{BL}} - \text{HbA1c}_{\text{NoEL}}) \quad (4)$$

Equation 4 is in the same form as Equation 1, with the same HbA1c<sub>NoEL</sub> value and a slope parameter given by

$$m_{\text{Rx1+Rx2}} = m_{\text{Rx1}} + m_{\text{Rx2}} - m_{\text{Rx1}} \times m_{\text{Rx2}}$$

Thus, the effective *m* parameter for the combined treatment is less than the sum of the *m* parameters for each individual treatment due to the  $-m_{\text{Rx1}} \times m_{\text{Rx2}}$  term. It can be shown that the same equation is obtained if Rx2 is applied first followed by Rx1 (as long as both treatments have the same value for HbA1c<sub>NoEL</sub>). If HbA1c<sub>BL</sub> is the same for all treatment arms, Equation 4 can then be rewritten as shown in Equation 5:

$$\Delta\text{HbA1c}_{\text{Rx1+Rx2}} = \Delta\text{HbA1c}_{\text{Rx1 alone}} + \Delta\text{HbA1c}_{\text{Rx2 alone}}$$

$$+ \frac{\Delta\text{HbA1c}_{\text{Rx1 alone}} \times \Delta\text{HbA1c}_{\text{Rx2 alone}}}{(\text{HbA1c}_{\text{BL}} - \text{HbA1c}_{\text{NoEL}})} \quad (5)$$

Note that Equations 4 and 5 provide formulas for predicting the efficacy of combination treatments *assuming no direct pharmacodynamic interactions* that either limit or enhance the efficacy of the combination treatment.

### Modelling Combination Treatment Efficacy for Other Treatment Combinations

Data from several previously reported initial combination treatment studies were compiled [2–10]. In each study, the reported mean ΔHbA1c in the monotherapy arms and baseline HbA1c values were used to predict the mean ΔHbA1c in the combination arms using the new model, and results were compared with the observed mean ΔHbA1c in the combination arms.

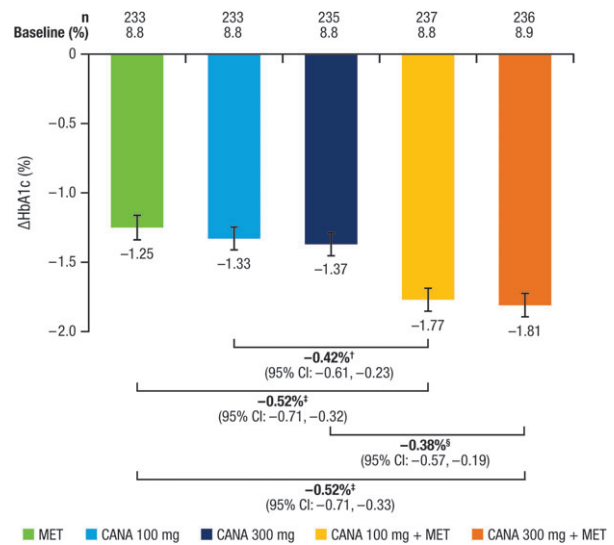
### Statistical Analyses

All regression and ANCOVA analyses were performed using MATLAB version 8.4.

## Results

### Patients in the Canagliflozin + Metformin Study

Patient characteristics were generally similar across treatment groups in the clinical study (Table S1) [11]. The mean baseline HbA1c ranged from 8.8 to 8.9% across groups. The mean duration of type 2 diabetes ranged from 2.9 to 3.5 years, and the mean estimated glomerular filtration rate ranged from 85 to 90 ml/min/1.73 m<sup>2</sup>.



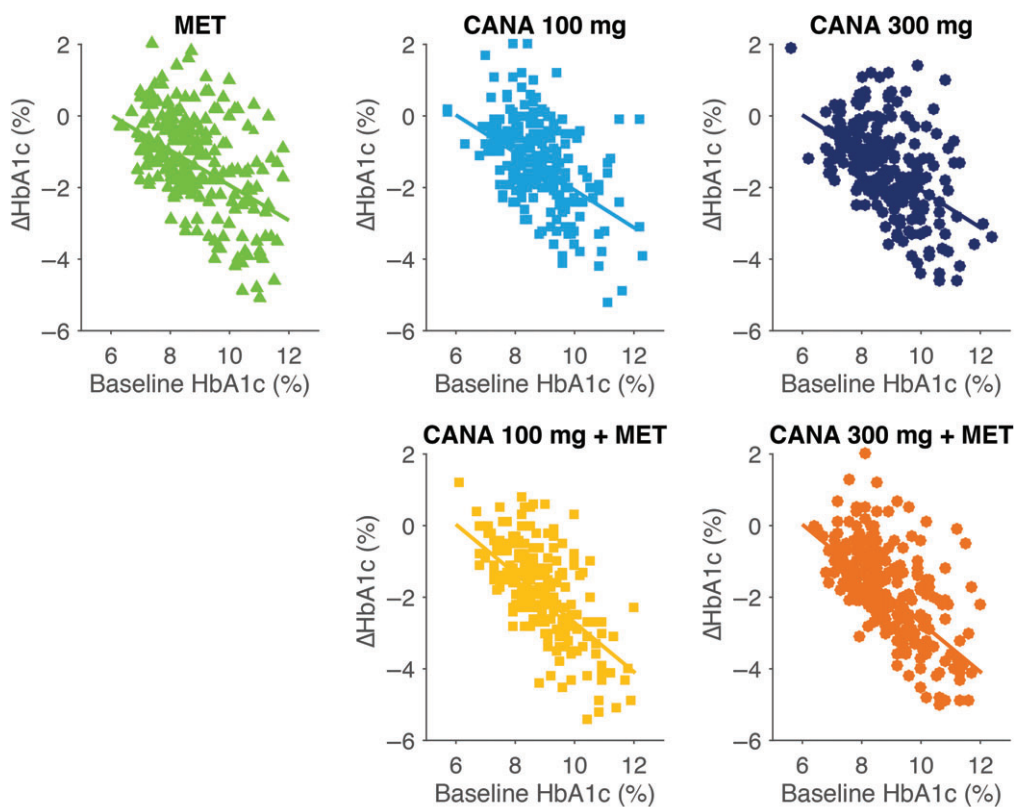
**Figure 1.** Change from baseline in HbA1c at week 26 (LOCF)\*. CANA, canagliflozin; CI, confidence interval; HbA1c, glycated haemoglobin; LOCF, last observation carried forward; LS, least squares; MET, metformin; s.e., standard error. \*Data are mean change ± s.e. from baseline. LS mean differences (95% CI) are shown for CANA 100 mg + MET and CANA 300 mg + MET versus their respective monotherapies. †p < 0.001 vs CANA 100 mg. ‡p < 0.001 vs MET. §p < 0.001 vs CANA 300 mg.

### Observed Reductions in HbA1c for Each of the Treatment Arms and Dependence on Baseline HbA1c

The observed reductions in HbA1c in each of the treatment arms of the canagliflozin + metformin study are shown in Figure 1. The efficacy for the combination arms, while greater than the efficacy of each of the individual treatment arms, was less than additive in both groups.

Within each treatment arm, greater reductions in HbA1c were seen in subjects with higher baseline HbA1c values, and the mean reductions in HbA1c approached 0 as HbA1c<sub>BL</sub> approached somewhere between 6.0 and 6.5%. When trying to estimate HbA1c<sub>NoEL</sub> separately for each of the three monotherapy arms, similar values were observed for each group [estimated HbA1c<sub>NoEL</sub> (95% confidence interval [CI]) = 6.49% (5.89, 7.09) for metformin, 6.43% (5.89, 6.08) for canagliflozin 100 mg and 6.24% (5.63, 6.86) with canagliflozin 300 mg]; therefore, the data for the three monotherapy arms were fit to a combined model based on Equation 1, using separate *m* parameters to characterize the efficacy for each treatment arm and a single HbA1c<sub>NoEL</sub> for all treatment arms [fitting the combined model gives HbA1c<sub>NoEL</sub> (95% CI) = 6.38% (6.05, 6.72)]. The data for the combination arms were subsequently fit using the same HbA1c<sub>NoEL</sub> level, again allowing for a separate *m* parameter for each of the combination treatment arms. The fit lines and the parameter values for each treatment arm are shown in Figure 2.

The estimated *m* values for each treatment can be interpreted as the fractional reduction in hyperglycaemia achieved by each treatment arm. For example, the estimated value of *m*<sub>MET</sub> is 0.52, meaning that, on average, metformin treatment provided a 52% reduction in the baseline elevation in HbA1c (defined as HbA1c<sub>BL</sub> - 6.38%). For example, subjects



**Best-fit Values (95% CI) of *m* for Each Treatment Arm**

| Monotherapy |                   | Combination therapy |                   |
|-------------|-------------------|---------------------|-------------------|
| MET         | 0.52 (0.44, 0.60) | CANA 100 mg + MET   | 0.73 (0.68, 0.77) |
| CANA 100 mg | 0.56 (0.47, 0.64) | CANA 300 mg + MET   | 0.70 (0.66, 0.75) |
| CANA 300 mg | 0.57 (0.48, 0.65) |                     |                   |

**Figure 2.** Relationship between change in HbA1c and baseline HbA1c in each treatment arm. CANA, canagliflozin; CI, confidence interval; HbA1c, glycated haemoglobin; MET, metformin.

with  $HbA1c_{BL} = 7.38\%$  would be predicted to see a mean  $\Delta HbA1c = -0.52\%$ , whereas subjects with  $HbA1c_{BL} = 10.38\%$  would be predicted to see a mean  $\Delta HbA1c = -2.08\%$ . As with the least squares (LS) mean reductions in HbA1c, the estimated *m* values for the combination treatment arms are less than the sum of the estimated *m* values of the individual treatment arms, thereby suggesting the subadditivity of effect in terms of the combination treatment arms.

### Predicting the Efficacy of Combination Arms Based on Monotherapy Efficacy

Applying Equation 4 to the observed canagliflozin + metformin data gives predicted efficacy for both combination arms that is within 10% of the observed mean values for both combination arms, whereas assuming additive efficacy would overpredict the observed mean efficacy by nearly 50% (Table 1); therefore, the efficacy observed with the combination canagliflozin + metformin arms is close to what is expected based on the efficacy of the individual arms and the impact of

baseline HbA1c on the treatment effect size, suggesting that there are little to no pharmacodynamic interactions between the two treatments that limit the efficacy of the combination beyond the limitation imposed by reduced  $\Delta HbA1c$  effects for all treatments as HbA1c approaches the normal range.

### Applicability of Analysis for Other Combination Treatment Studies

Several other fixed-dose combination studies have been published comparing the efficacy of initial combination treatment with the efficacy in each of the monotherapy arms [2–10]. The observed results from a number of these studies are shown in Table 2, along with the predicted efficacy obtained using Equation 5 and also assuming simple additivity. As in the canagliflozin + metformin study that is analysed in detail here, Equation 5 provides a much more accurate prediction of the efficacy of combination treatment (mean predicted  $\Delta HbA1c = -1.67\%$  using Equation 5 vs mean observed  $\Delta HbA1c = -1.72\%$ ) than what would be obtained



**Table 1.** Observed and predicted HbA1c values.

| Treatment arm     | Mean (s.d.) baseline HbA1c, % | Observed mean $\Delta$ HbA1c (s.d.), % | Predicted $\Delta$ HbA1c using Equation 4, % | Predicted $\Delta$ HbA1c if additive efficacy, % |
|-------------------|-------------------------------|--|--|--|
| CANA 100 mg + MET | 8.82 (1.10)                   | -1.77 (1.28)                           | -1.97  | -2.68  |
| CANA 300 mg + MET | 8.90 (1.21)                   | -1.81 (1.29)                           | -2.02  | -2.73  |

CANA, canagliflozin; HbA1c, glycated haemoglobin; MET, metformin; s.d., standard deviation.

by assuming additivity (mean predicted  $\Delta$ HbA1c = -2.19%). A similar conclusion is reached if the mean across studies is weighted by the number of participants in each of the studies (weighted mean  $\Delta$ HbA1c = -1.82% for observed values vs -1.78% for predictions using Equation 5 and -2.36% for predictions using simple additivity). The mean percentage difference between the predicted and observed values was 8.6% when using Equation 5 and 27.0% when assuming additivity.

## Discussion

Consistent with studies of other combination therapies [2–10], initial combination therapy with canagliflozin and metformin was associated with larger reductions in HbA1c compared with each treatment as monotherapy; however, the observed changes in HbA1c were smaller in magnitude than expected based on a simple additivity model for changes with each treatment individually. The quantitative model described in the present paper gives a clear explanation of why combination treatment with canagliflozin and metformin, as well as other combination treatments, results in subadditive efficacy because of differences in the effective baseline HbA1c on which each treatment acts when given as part of a combination treatment, compared with when the treatments are given alone. Using data from each monotherapy component, this model can be used to predict the glycaemic efficacy of combination therapies with greater accuracy than simple additivity, with predictions for the efficacy for the combination treatment arms falling within 10% of the observed values for most of the combinations tested. The most notable difference between the observed changes in HbA1c and the predictions obtained using Equation 5 was from the 24-week study with initial combination treatment with metformin + sitagliptin [8], where the efficacy of the combination treatment was closer to being additive than that which was predicted using Equation 5. As shown in Table 2, the near-additivity seen in this study at 24 weeks was not seen at later time points in this same study [9,10] and also was not seen at 24 weeks in the metformin + saxagliptin study [6], suggesting that the finding of near-additivity seen with metformin + sitagliptin at 24 weeks is not a general finding with metformin + DPP-4 inhibitor combination treatment.

In summary, the findings from the present analysis show why combination therapy for type 2 diabetes is generally expected to have subadditive efficacy, even in the absence of direct pharmacodynamic interactions. This model can be applied to assess any potential synergistic or antagonistic interactions between treatments to be used in combination by comparing the observed

efficacy with the expected efficacy based on individual treatment arms.

Using this model and reporting the parameters of  $m$  and  $HbA1c_{NoEL}$  for individual treatments has potential to be useful on its own, as these parameters provide a description of efficacy that is largely independent of the mean baseline HbA1c value in the study. By contrast, the commonly reported values of mean  $\Delta$ HbA1c and the proportion of subjects achieving HbA1c <7% are heavily influenced by the baseline HbA1c in the study, making cross-study comparisons difficult to interpret.

The critical assumption used in the present analysis is that the two different scenarios of simultaneous combination treatment or sequential treatment leading to the same combination will both provide the same efficacy. Although this assumption has not been generally tested for combination treatments, it is consistent with recently reported data from phase III studies with dapagliflozin and saxagliptin; studies where the combination was given by first treating with dapagliflozin and then adding on saxagliptin [12], or by first treating with saxagliptin and then adding on dapagliflozin [13], gave similar total efficacy, as was seen in a previous study in which dapagliflozin and saxagliptin were given together as initial combination treatment [5]. In general, this assumption seems reasonable, as long as the treatment time required for steady-state efficacy is relatively short compared with the rate of disease progression. Equations 4 and 5 require both treatments to have the same  $HbA1c_{NoEL}$  value; if the two treatments have different  $HbA1c_{NoEL}$  values, then the efficacy of the combination treatment that would be predicted using the method described would ultimately depend on the order in which the two agents were applied. A limitation of the present analysis is that the calculations only provide steady-state efficacy predictions and do not predict the time profile associated with HbA1c changes for the combination treatments. Another limitation of this analysis is its use of data only from randomized controlled trials, which each included specific patient populations defined by study eligibility criteria. Because of the selective nature of such trials, it is possible that the efficacy of combination therapy in more diverse populations in real-world settings may differ somewhat from that which was observed in the clinical trial setting.

In summary, the efficacy of combination therapies for type 2 diabetes is influenced by multiple factors, including baseline HbA1c. This study reports a quantitative method to determine the efficacy of combination therapies using data from individual monotherapy treatments, by modelling how applying one treatment lowers the 'effective baseline HbA1c' for a second treatment under the assumptions of reaching steady

**Table 2.** Observed and predicted changes in HbA1c with combination therapies in previous studies.

| Combination treatment             | Patients, N | Baseline HbA1c, % | Observed $\Delta$ HbA1c, %    | Predicted $\Delta$ HbA1c using Equation 5, *% | Predicted $\Delta$ HbA1c if additive efficacy, % | References |
|-----------------------------------|-------------|-------------------|-------------------------------|---|--|------------|
| DAPA 5 mg + MET                   | 185         | 9.2               | -2.05 (95% CI: -2.23, -1.88)† | -1.97   | -2.54  | [2]        |
| DAPA 10 mg + MET                  | 202         | 9.1               | -1.98 (95% CI: -2.13, -1.83)† | -2.12   | -2.89  | [2]        |
| ALO 25 mg + PIO 30 mg             | 164         | 8.8               | -1.71 (0.081)‡                | -1.65   | -2.11  | [4]        |
| DAPA 10 mg + SAXA 5 mg            | 158         | 8.9               | -1.47 (95% CI: -1.62, -1.31)† | -1.66   | -2.08  | [5]        |
| EMPA 10 mg + LINA 5 mg            | 135         | 8.0               | -1.08§                        | -1.07   | -1.36  | [3]        |
| EMPA 25 mg + LINA 5 mg            | 134         | 7.9               | -1.19§                        | -1.03   | -1.32  | [3]        |
| SAXA 10 mg + MET                  | 315         | 9.5               | -2.5§                         | -2.60   | -3.70  | [6]        |
| ALO 25 mg + MET                   | 114         | 8.4               | -1.55 (0.090)‡                | -1.36   | -1.67  | [7]        |
| SITA 100 mg + MET                 | 178         | 8.8               | -1.90 (95% CI: -2.06, -1.74)¶ | -1.48   | -1.79  | [8]        |
| SITA 100 mg + MET                 | 153         | 8.7               | -1.8 (95% CI: -2.0, -1.7)#    | -1.65   | -2.10  | [9]        |
| SITA 100 mg + MET                 | 105         | 8.6               | -1.7 (95% CI: -1.8, -1.5)**   | -1.80   | -2.5   | [10]       |
| <b>Mean (s.e.) across studies</b> |             |                   | <b>-1.72 (0.12)</b>           | <b>-1.67 (0.14)</b>                           | <b>-2.19 (0.21)</b>                              |            |

ALO, alogliptin; CI, confidence interval; DAPA, dapagliflozin; EMPA, empagliflozin; HbA1c, glycated haemoglobin; LINA, linagliptin; LS, least squares; MET, metformin; PIO, pioglitazone; SAXA, saxagliptin; s.e., standard error; SITA, sitagliptin.

\*Calculations with Equation 5 were based on  $HbA1c_{NoEL} = 6.4\%$ .

†Data are mean change (95% CI) from baseline at week 24.

‡Data are LS mean change (s.e.) from baseline at week 26.

§Data are adjusted mean change from baseline at week 24.

||All three SITA 100 mg + MET results are from the same study, with the different rows reflecting results from different time points (i.e. 24, 54 and 104 weeks).

¶Data are LS mean change (95% CI) from baseline at week 24.

#Data are LS mean change (95% CI) from baseline at week 54.

\*\*Data are LS mean change (95% CI) from baseline at week 104.

state and no direct pharmacodynamic interactions. This analysis provides insight into why subadditivity of  $\Delta$ HbA1c is frequently observed with combination treatments for type 2 diabetes and shows that subadditivity is expected to occur even when there are no direct detrimental pharmacodynamic interactions.

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## Conflict of Interest

D. P., G. C. and R. Q. are full-time employees of Janssen Research & Development, LLC.

D. P. and R. Q. contributed to the design and conduct of the study, the acquisition, analysis and interpretation of the data, and development of the manuscript. G. C. contributed to the analysis and interpretation of data and development of the manuscript. All authors approved the final version of the submitted manuscript.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Baseline Demographic and Disease Characteristics [11]

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