Technical Appendix to:
A novel model-based meta-analysis to indirectly estimate the comparative efficacy of two medications: an example using DPP-4 inhibitors, sitagliptin and linagliptin, in treatment of type 2 diabetes mellitus

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This appendix is intended primarily to provide a mathematical / statistical specification of the final model employed in our analysis. We additionally mention several variants of the model that were considered during model development.

1 Base model: structural form

The structural form of the model (i.e., the parametric form relating the central tendency of predictions to time, dose, and covariates) remained largely unchanged across all model-fitting iterations described in the present report. This structural form may conceptualized in terms of a latent (random-effect) baseline HbA1c ($\text{HbA1c}_{\text{base}}$) that is modified as a function of dose (D) and time (t) by multiplicative terms for the effect of washout, placebo intervention, and drug effect (where applicable).

$$\begin{aligned}
\text{HbA1c}(t,D) \;=\; & \text{HbA1c}_{\text{base}} \\
& \times I_{\text{washout}} \frac{\left(1+\Delta W_{\infty}\left(1-e^{-k_W(t+t_{\text{wash}})}\right)\right)}{1+\Delta W_{\infty}\left(1-e^{-k_W t_{\text{wash}}}\right)} && \text{(washout effect)} \\
& \times \left(1+\Delta P_{\infty}\left(f^{P}(t)\right)\right) && \text{(placebo effect)} \\
& \times \left(1-\frac{E_{\max,\text{drug}} D}{ED_{50,\text{drug}}+D}\left(1-e^{-k_{\text{drug}} t}\right)\right) && \text{(drug effect)}
\end{aligned}$$

We now consider each of the model terms in slightly more detail:

- Washout term

  $$\frac{\left(1+\Delta W_{\infty}\left(1-e^{-k_W(t+t_{\text{wash}})}\right)\right)}{1+\Delta W_{\infty}\left(1-e^{-k_W t_{\text{wash}}}\right)}$$

  Although response observations from the (pre-treatment) washout period were not modeled, the duration of pre-treatment washout t_{wash} is used to determine how much of the post-baseline trend can be attributed to washout. One may better understand the washout term in terms of the following two extreme scenarios:

  - The washout term for a group with an extremely long pre-treatment washout ($t_{\text{wash}} \approx \infty$) would be essentially 1, i.e., no adjustment.
  - The washout term for a group discontinuing prior medication only at the time of the first dose of the randomized treatment ($t_{\text{wash}} \approx 0$) would be $\left(1+\Delta W_{\infty}\left(1-e^{-k_W(t)}\right)\right)$, a term that rises exponentially from 1 (no adjustment at baseline) toward a horizontal asymptote of $(1+\Delta W_{\infty})$ as t becomes very large.

  As a conceptual and notational device, we also define $\text{HbA1c}_{\text{prior}}$, the inferred HbA1c level at the beginning of the washout period:

  $$\text{HbA1c}_{\text{prior}} \equiv \frac{\text{HbA1c}_{\text{base}}}{1+\Delta W_{\infty}\left(1-e^{-k_W t_{\text{wash}}}\right)}$$

- Placebo term $\left(1+\Delta P_\infty\left(f^P(t)\right)\right)$. Both exponential and a bi-exponential variants were considered for f^P:

$$\begin{aligned} f^P(t) &= 1-e^{-k_P t} && \text{("exponential" variant)} \\ f^P(t) &= e^{-k_{P0} t}-e^{-k_P t} && \text{("bi-exponential" variant)} \end{aligned}$$

The placebo term is intended to characterize all aspects of the longitudinal profile that are common to all placebo-treated patients. In principal at least, this may include more than a mere "placebo effect". For example, it might also partially reflect longitudinal changes that would occur even in the absence of placebo intervention. In contrast to the washout term, the placebo term does not vary systematically as a function of washout duration (in particular, in contrast to the washout term, the placebo "effect" does not approach a limit of zero as washout duration approaches infinity), so that the two effects are distinctly identifiable.

The exponential and bi-exponential variants of the placebo function have different implications with respect to the limiting placebo effect P_∞ at large time values. The bi-exponential variant, sometimes referred to as a "Bateman" function is a typical choice in the pharmacology domain for modeling placebo effects, and is applicable when placebo effects are expected to return to zero at some duration [4]. By contrast, our "exponential" variant implies a non-zero limiting effect due to placebo. In practice, the predictive implications for the fitted model may be similar for both functions over a finite duration of interest, since the estimated parameters in the Bateman function may (if supported by the data) imply a positive first derivative over most or all of that duration (in our case, over a 24 week duration). To the extent that data do not support any return to zero for the placebo effects over the duration of interest, both convergence diagnostics and model selection criteria will tend to favor the simpler "exponential" placebo function. In our application the bi-exponential / Bateman functional form appeared to be reasonably well estimated and so was therefore employed in the final model.

As a conceptual and notational device, we also define $\text{HbA1c}_{\text{placebo}}(t)$, the expected time course for an individual randomized to placebo:

$$\begin{aligned} \text{HbA1c}_{\text{placebo}}(t) &= \text{HbA1c}_{\text{base}} \\ &\quad \times I_{\text{washout}}\frac{\left(1+\Delta W_\infty\left(1-e^{-k_W(t+t_{\text{wash}})}\right)\right)}{1+\Delta W_\infty\left(1-e^{-k_W t_{\text{wash}}}\right)} && \text{(washout effect)} \\ &\quad \times\left(1+\Delta P_\infty\left(f^P(t)\right)\right) && \text{(placebo effect)} \end{aligned}$$

Further, we define HbA1c_∞ to be the limiting value of $\text{HbA1c}_{\text{placebo}}(t)$ as t becomes very large.

- Drug effect term

$$(1-E_{\text{drug}}) \equiv \left(1-\frac{E_{\max,\text{drug}} D}{ED_{50,\text{drug}}+D}\left(1-e^{-k_{\text{drug}} t}\right)\right)$$

This term varies as a function of both dose (D) and time (t). The term equals 1 (no adjustment) when $t=0$ and/or $D=0$, and approaches a horizontal asymptote of $(1-E_{\max,\text{drug}})$ as both D and t become very large. The parameter k_{drug}, which describes the onset of drug effects, was provisionally assumed

to take the same value for both linagliptin and sitagliptin, consistent with the expected pharmacology of the two DPP4 inhibitors (empirical support for this assumption is provided by the posterior predictive checks included in the primary manuscript).

The dose-response component of our model may be described as a simplified E_{max} model, a more general expression of which is:

$$E = \frac{E_{max} D^{\alpha}}{ED_{50}^{\alpha} + D^{\alpha}}.$$

This functional form, also known as the Hill Equation, is widely used in the pharmacology domain to describe both concentration-response and dose-response relationships [5]. Originally proposed on the basis of drug receptor theory to describe concentration-response analyses, its use in describing dose-response relationships may also be theoretically justified when linear pharmacokinetics apply and dose is therefore an appropriate proxy for concentration. Theoretical support is more tenuous when nonlinear pharmacokinetics apply (as is the case for linagliptin), but the model remains a reasonable initial default. The parameter α, sometimes referred to as the Hill coefficient or the sigmoidicity parameter, has been set to a value of 1 in our implementation. This simplification was initially introduced on a tentative basis, in consideration of the limited degree of dose-response information in the data, and based on prior experiences of the modeling team suggesting that, empirically, the Hill coefficient for dose-response relationship is generally close to one. This simplification does imply a dose-response relationship that has a non-zero gradient at $D = 0$, however this implication is consistent with observed dose-response relationships (anecdotally) for most drugs. Final acceptance of this aspect of the model was based on the observed predictive performance of our model at all studied dose levels.

We may now use the terms introduced above to define the conditional expectation for the mean HbA1c on the i^{th} occasion in the j^{th} group and k^{th} study:

$$\begin{aligned}
\widehat{\text{HbA1c}}_{ijk} &= \text{HbA1c}_{\text{prior},jk} \\
&\quad \times \left(1 + \Delta W_{\infty,jk} \left(1 - e^{-k_W\left(t_{ijk} + t_{\text{wash},jk}\right)}\right)\right) \\
&\quad \times \left(1 + \Delta P_{\infty,jk} \left(f^P(t_{ijk})\right)\right) \\
&\quad \times \left(1 - \frac{E_{\max,\text{drug}_{jk}} D_{jk}}{ED_{50,\text{drug}_{jk}} + D_{jk}} \left(1 - e^{-k_{\text{drug}} t_{ijk}}\right)\right)
\end{aligned}$$

Note that the circumflex, or "hat", has not been used here to indicate an estimate (as would be common in the statistical literature), but refers rather to an expected value (as is common in the pharmacometric literature).

2 Base model: stochastic structure

Random effects associated with washout and placebo effects were implemented using a re-parameterization of the model. The parameters ΔW_{∞} and ΔP_{∞} represent conceptual steady state asymptotes for very large

time values ($t \to \infty$). Since it is not clear that direct estimation of such parameters is supported by the data, the model was implemented using truncated parameterizations that reformulate the effect parameter as an effect at a time t^* that is richly represented in the data set. For this purpose we define ΔW^* and ΔP^* as the fractional changes at reference time $t^* = 24$ weeks due to washout and placebo, respectively. That is,

$$\begin{aligned} \Delta W^* &= \frac{\left(1 + \Delta W_\infty \left(1 - e^{-k_W (t^* + t_{\text{wash}})}\right)\right)}{1 + \Delta W_\infty \left(1 - e^{-k_W t_{\text{wash}}}\right)} - 1 \\ \Delta P^* &= \Delta P_\infty f^P(t^*). \end{aligned}$$

The random-effect structure for the i^{th} visit for the j^{th} arm (or group) in the k^{th} study may then be described as:

Inter-study variation:

$$\log\left(1 + \Delta P^*_{\text{study},k}\right) \sim N\left(\log\left(1 + \widehat{\Delta P^*}\right), \psi^2_{\Delta P}\right)$$

Study-level random effects are additionally considered for mean baseline HbA1c and for the washout magnitude ΔW^*, but convergence diagnostics suggested that this level of variation in these parameters was not identifiable based on the available data.

All study-level random effects are assumed to be independent.

Inter-arm variation:

$$\begin{aligned} \log\left(1 + \Delta P^*_{jk}\right) &\sim N\left(\log\left(1 + \Delta P^*_{\text{study},k}\right), \omega^2_{\Delta P}/n_{1jk}\right) \\ \log\left(\text{HbA1c}_{\text{base},jk}\right) &\sim N\left(\log\left(\text{HbA1c}_{\text{base-study},k}\right), \omega^2_{\text{HbA1c}_{\text{base}}}/n_{1jk}\right) \end{aligned}$$

All arm-level random effects are assumed to be conditionally independent, given study-level random effects. Our scaling of random effect variances according to sample size follows a recently published rationale [1], and is similar to an approach used in model-based meta-analysis of Alzheimer's Disease progression [3]. Arm-level random effects were additionally considered for the washout magnitude ΔW^*, but convergence diagnostics suggested that this level of variation was also not identifiable based on the available data.

Modeling baseline HbA1c values using Lognormal distributions constrains these to positive values. Modeling the Δ parameters using shifted Lognormal distributions allows the placebo and washout factors in the model to take positive and negative (up to negative one) values. Taken together with constraints on the drug effects (ensured via the prior for the drug $E_{\max}$ values), and the multiplicative construction of the model, the preceding constraints ensure that all HbA1c predicted values are positive.

Residual variation:

$$\text{HbA1c}_{ijk} \sim N\left(\widehat{\text{HbA1c}}_{ijk}, \frac{\sigma^2}{n_{ijk}}\right).$$

3 Covariates

Baseline HbA1c
Baseline HbA1c is implicitly included as a covariate in the model in the sense that the washout, placebo, and drug effect terms all operate multiplicatively on baseline HbA1c. In general, larger changes from baseline are implied by larger baseline values.

Washout
The inclusion of the washout term in the base model implies that washout status and washout duration act as covariates in the sense that they modify an individual's predicted change from baseline.

Other covariates

Whereas the covariate effects of baseline HbA1c and washout duration are implied by the longitudinal structure of the base model, the remaining candidate covariates were considered as potential modifiers of drug effect in a manner dependent on the covariate variable's distributional properties.

- For univariate covariates taking discrete values at the arm-level (as was the case with background medication status), the covariate effect was introduced via an exponentiated linear predictor so that, with x_{jk} denoting the dichotomous variable level on arm j in study k, the following substitution is made:
$$E_{\text{max,drug}_{jk}} \leftarrow E_{\text{max,drug}_{jk}} \times \exp\left\{\beta_{\text{drug}_{jk}} x_{jk}\right\}$$
(This approach is equivalent, modulo re-parameterization, to simply using a different $E_{\text{max,drug}}$ for each level of the covariate.)

- For univariate covariates taking continuous values at the arm-level including age, body mass index (BMI), gender (recall that at the arm-level, gender is represented as a proportion), and duration of diabetes, the candidate covariate was centered at its average value and an exponentiated linear predictor was again used. In this case, letting x_{jk} be the continuous covariate, the following substitution is made:
$$E_{\text{max,drug}_{jk}} \leftarrow E_{\text{max,drug}_{jk}} \times \exp\left\{\beta_{\text{drug}_{jk}} (x_{jk} - \overline{x_{\cdot\cdot}})\right\}.$$

- Race, like gender, is represented at the arm-level using proportions. However, unlike gender, the racial composition of a each study arm must be represented with *multiple* proportions (specifically, proportion white, proportion black, proportion asian, and, in certain cases, proportion "other"), precluding any interpretable use of the continuous covariate parameterization that was used for gender. Instead, a separate $E^r_{\text{max,drug}_{jk}}$ was defined for each race r (separately for each drug). Race-specific terms in the model then imply race-specific conditional expectations $\widehat{\text{HbA1c}}^r_{ijk}$, and the aggregate conditional expectation is computed using a weighted average:
$$\widehat{\text{HbA1c}}_{ijk} = \sum_{r \in (\text{white, black, asian, other})} F^r_{ijk} \widehat{\text{HbA1c}}^r_{ijk}$$
where F^r is the fraction of the arm identifying with race r.

  In order to improve parameter estimation for race-based covariate effects, racially subsetted data were used where possible (this was possible in all cases for linagliptin records).

As noted in the primary manuscript, the effects of covariates other than race were not sufficiently well estimated to justify inclusion in the model. Race was therefore the only explicit in the final model (in addition to the implicit covariates, baseline HbA1c and washout duration).

4 Priors

The probabilistic specification of the prior is provided in Table 1. With regard to the primary research questions of interest, the most consequential components of the prior are the distributional statements relating to the magnitudes of drug effects, $E_{\text{max, linagliptin}}$ and $E^*_{\text{max, sitagliptin}}$. Since those parameters represent asymptotic drug effects (at theoretically infinite times), we re-parameterize in terms of effects at 24 weeks, $E^*_{\text{linagliptin}}$ and $E^*_{\text{sitagliptin}}$, using the same reasoning as was discussed for placebo and washout effects. Since these drug effect parameters represent fractional reductions from a hypothetical untreated state, it is natural that they should be bounded between zero and one, implying that both drugs have some beneficial effect (a defensible assumption for marketed drugs), neither or which may reduce HbA1c levels below zero (patently true). The use of Uniform (flat) densities between these two extremes implies that all intermediate values are considered (*a priori*) equally likely. Perhaps most importantly, the distributions for $E^*_{\text{linagliptin}}$ and $E^*_{\text{sitagliptin}}$ are specified as being independent. In combination with the use of Uniform densities, the prior independence of these two parameters allows for potential findings of either substantial similarity or substantial difference between the two drugs, as determined by the data.

Priors for ancillary (non-drug-effect) parameters were chosen largely for analytical convenience, but were verified to be diffuse in comparison to thier corresponding posterior distributions, suggesting that these elements of the prior were sufficiently non-informative. Additionally, alternative distributions were evaluated for a number of elements of the prior (e.g. for variance components), and did not result in any substantial differences in conclusions.

parameter	prior
k_W (w^{-1})	Unif$(0.001, 7)$
k_{P0} (w^{-1})	Unif$(0.001, 7)$
k_P (w^{-1})	Unif$(0.001, 7)$
k_{drug} (w^{-1})	Unif$(0.001, 7)$
$\widehat{\text{HbA1c}_{\text{base}}}$	Log Normal$(0, 100)$
$\widehat{\Delta W^*}$	Unif$(-1, 10)$
$\log\left(1+\widehat{\Delta P^*}\right)$	Unif$(-10, 5)$
$\psi_{\Delta P}$	Unif$(0, 10)$
$\omega_{\Delta P}$	Unif$(0, 10)$
ω_{HbA1c_0}	Unif$(0, 5)$
σ	Unif$(0, 100)$
$b_{\text{linagliptin}}$	Unif$(0, 100)$
$b_{\text{sitagliptin}}$	Unif$(0, 100)$
$E^*_{\text{linagliptin}}$	Unif$(0, 1)$
$E^*_{\text{sitagliptin}}$	Unif$(0, 1)$
$E_{\text{max,linagliptin}}$	$(\frac{1}{b_{\text{linagliptin}}}+1) * E^*_{\text{linagliptin}}$
$E_{\text{max,sitagliptin}}$	$(\frac{1}{b_{\text{sitagliptin}}}+1) * E^*_{\text{sitagliptin}}$
$ED_{50,\text{linagliptin}}$	$\frac{10}{b_{\text{linagliptin}}}$
$ED_{50,\text{sitagliptin}}$	$\frac{200}{b_{\text{sitagliptin}}}$

Table 1: Prior distribution for parameters in base model

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