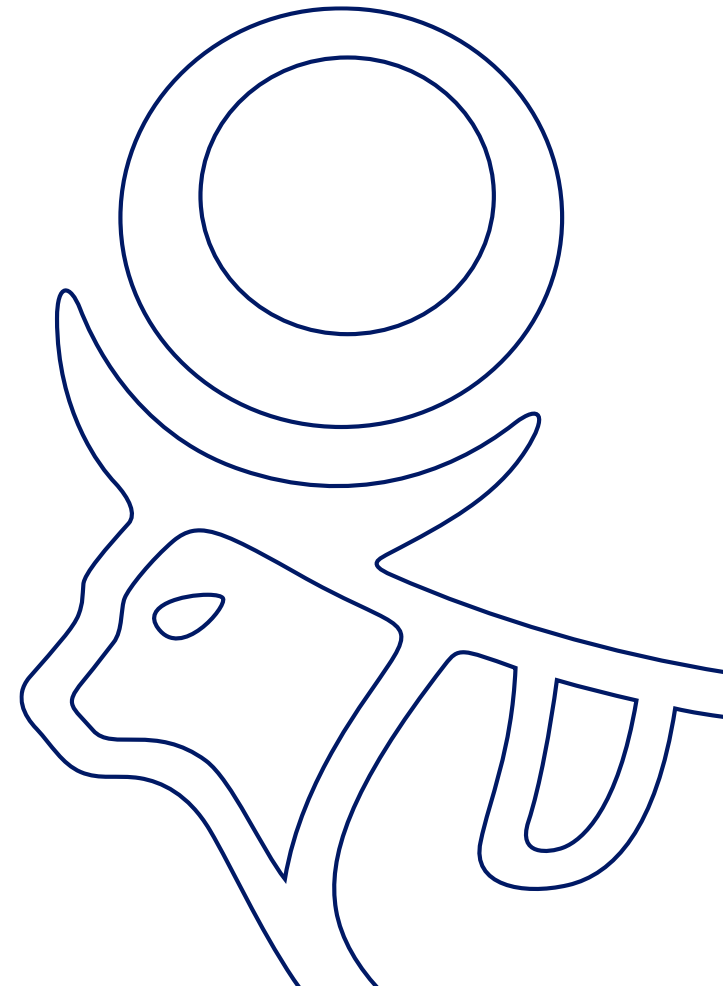


Model-Based Network Meta-Analysis

Integrating time-course and dose-response modeling

Anders Strathe, **Martin Bøg**, Anders Gorst-Rasmussen
Novo Nordisk A/S

24-OCT-2025



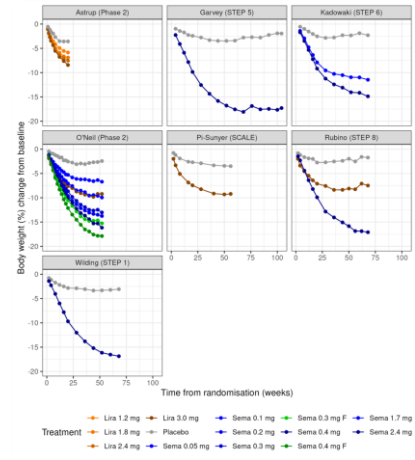
Questions in drug development and HTA

Portfolio Decision Making

- How can we combine our current evidence to predict Ph3 efficacy for different doses?
- What dose should we pick for phase 3 in order to be competitive with other treatments?
- Based on our 26 week study what treatment effects do we expect to see at 68 weeks?
- Should we conduct a Phase 3b head-to-head study vs our competitor?
- This treatment just published their Phase 2. Should we expect them to go to Phase 3 and be competitive?

Indirect Treatment Comparisons for HTA

- The outcome for this treatment is only reported at 60 weeks, while others report at 68 weeks. Should we exclude the evidence?
- We are also interested in treatment effects at 26 weeks to align with HE modeling but comparator X only reports their Ph3 at 68 weeks. What should we do?
- What treatments effects can we expect after 2 years of treatment?
- Should we exclude this dose from the analysis as it is not a licensed dose?
- Can we reduce uncertainty for the licensed doses by including our Phase 2 data?



Time-course and dose-response relationships are promising targets for borrowing to reduce evidence gaps




What do we add?

- Previous research has provided formulations of time-course and dose-response as separate model formulations
- We build on this work and provide a model-based network meta-analysis framework that integrates time-course and dose-response modeling
- We simulate a trial program including a competitor program, and show that our formulation can recover the data generating parameters (see paper)
- We illustrate the method on a treatment network for weight management

<https://doi.org/10.1002/psp4.12091>

<https://doi.org/10.1002/jrsm.1351>

CPT: Pharmacometrics & Systems Pharmacology

Original Article |  Open Access |  

Model-Based Network Meta-Analysis: A Framework for Evidence Synthesis of Clinical Trial Data

D Mawdsley  M Bennetts, S Dias, M Boucher, NJ Welton



First published: 01 August 2016 | <https://doi.org/10.1002/psp4.12091> | Citations: 83

Received: 14 March 2018 | Revised: 12 December 2018 | Accepted: 11 April 2019
DOI: 10.1002/jrsm.1351

RESEARCH ARTICLE

WILEY Research
Synthesis Methods

Modelling time-course relationships with multiple treatments: Model-based network meta-analysis for continuous summary outcomes

Hugo Pedder¹  | Sofia Dias¹  | Margherita Bennetts²  | Martin Boucher² | Nicky J. Welton¹ 

A random-effects (exchangeable) NMA for a continuous summary measure

- Studies $i = 1, \dots, I$
- Treatments $j = 1, \dots, J$ (*treatment 1 is the reference*)

$$y_{ij} \sim N(\mu_i + \delta_{ij}, se_{ij}^2)$$
$$\delta_{ij} \sim N(d_j, \tau^2)$$

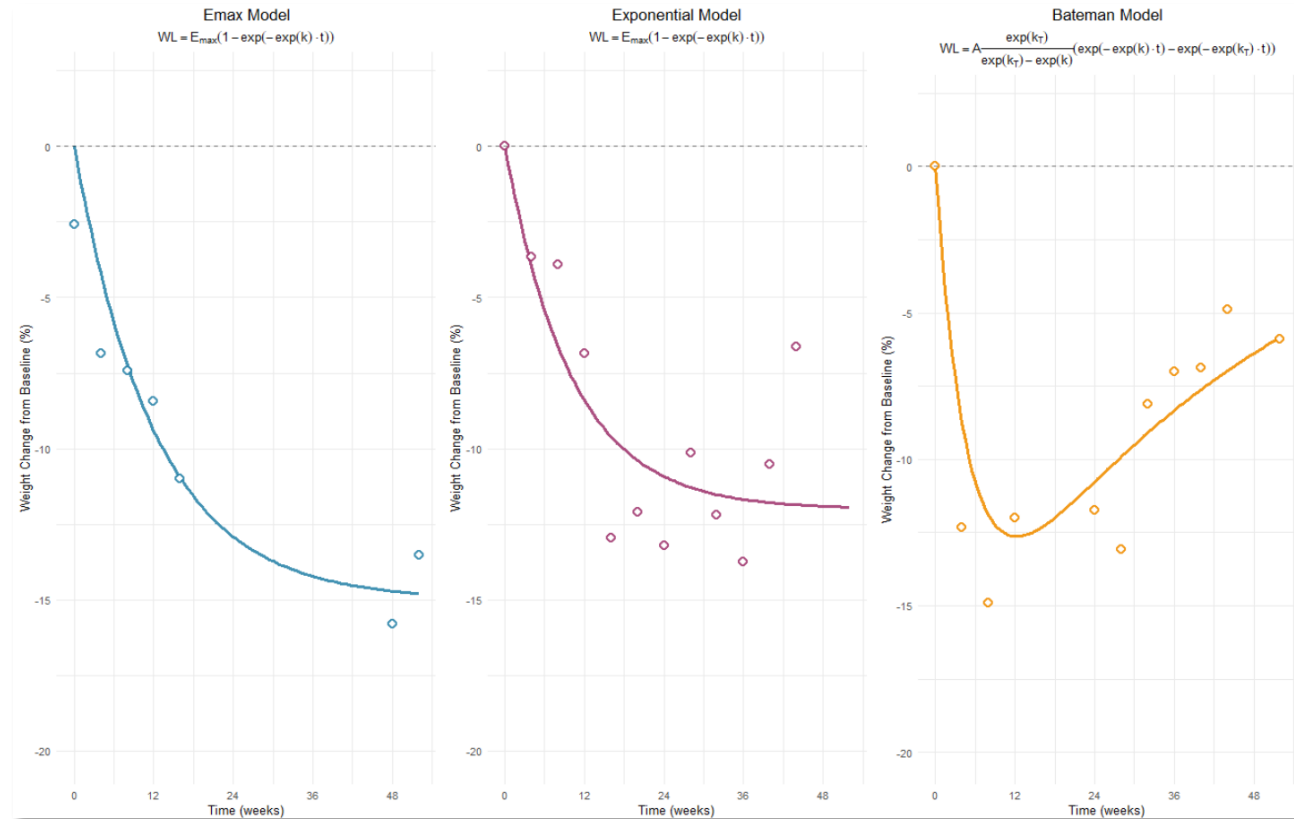
consistency: $d_{ab} = d_{1b} - d_{1a}; a, b \in \{2, \dots, J\}; d_1 = 0$

Time-course modeling

Model	Function: $f(\cdot)$	Parameters
E _{max}	$E_{max} \frac{t}{\exp(ET_{50}) + t}$	E_{max} and $\log(ET_{50})$
Exponential	$E_{max}(1 - \exp(-\exp(k) \times t))$	E_{max} and $\log(k)$
Bateman	$A \left(\frac{\exp(kT)}{\exp(kT) - \exp(k)} \right) (\exp(-\exp(k) \times t) - \exp(kT) \times t)$	A, $\log(k)$ and $\log(kT)$

t: time in weeks

Positive parameters (i.e. k, kT, ET₅₀) expressed on log scale

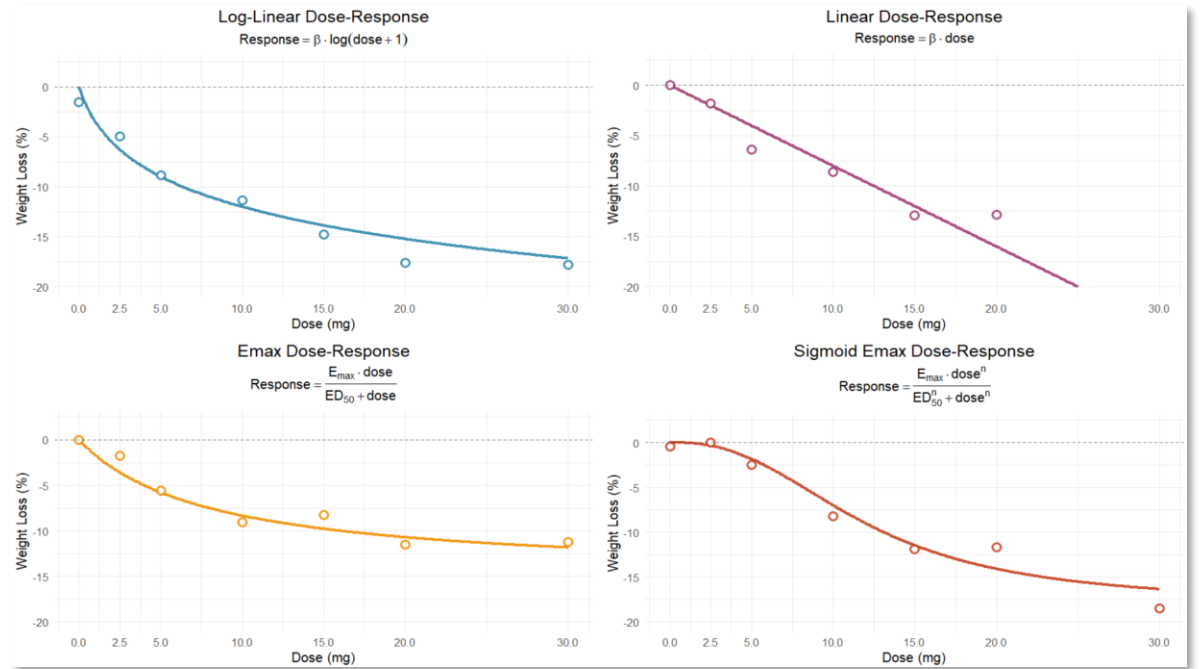


Dose-response Modeling

Model	Function: $f(\cdot)$	Parameters
Log-linear	$\beta \times \log(d + 1)$	β
Linear	$\beta \times d$	β
E _{max}	$E_{max} \frac{d}{\exp(ED_{50}) + d}$	E_{max} and $\log(ED_{50})$
Sigmoid E _{max}	$E_{max} \frac{d^n}{\exp(ED_{50})^n + d^n}$	E_{max} , $\log(ED_{50})$, $n > 0$

d: Dose in mg

Positive parameters (e.g. ED_{50}) were expressed on a log scale



Time-course dose-response NMA for continuous summary measures

- Extend the standard NMA model to include multiple time points
- Let \mathbf{y}_{ij} denote a *vector* of continuous summary measure for study ($i = 1, \dots, I$) and arm ($j = 1, \dots, n_i$) of the time-course profile ($t = [0, \dots, T_{ij}]$), for example % change from baseline in body weight
- We assume that :

$$\mathbf{y}_{ij} \sim MVN(\boldsymbol{\mu}_{ij}, \boldsymbol{\Sigma}_{ij})$$

- $\boldsymbol{\mu}_{ij}$ is the vector of mean outcomes
- $\boldsymbol{\Sigma}_{ij}$ is a covariance matrix, with diagonal elements within arm standard errors (se_{ij}), off-diagonals are either assumed to be 0, or to follow an AR(1) following Pedder, et al.

Embedding dose-response in the time-course model

- We put structure on the relationship for the p 'th structural parameter ($\theta_{ij}^{(p)}$) of the time course :

$$g\left(\theta_{ij}^{(p)}\right) = \begin{cases} \mu_i^{(p)} & j = 1 \text{ (reference)} \\ \mu_i^{(p)} + f(\mathbf{X}_{ij}\boldsymbol{\beta}^{(p)}, d_{ij}) + \gamma_{ij}^{(p)} & j > 1 \end{cases}$$

- $g(\cdot)$ is a link function, e.g. $\log(\cdot)$
- $\mu_i^{(p)}$ is the study specific level for the reference treatment in the i^{th} study
- $f(\cdot)$ is a parametric dose-response function, mapping the treatment doses to relative treatment effects and \mathbf{X}_{ij} is a design matrix, encoding agent specific effects and $\boldsymbol{\beta}^{(p)}$ is a vector of agent specific parameters
- The $\gamma_{ij}^{(p)}$ are random effects Let $\boldsymbol{\gamma}_i$ be of vector of study specific random effects of length $n_i - 1 \times n_p$, where n_p is the number of structural parameters (e.g. 3 for the Bateman model, Table 1). Then, it is assumed:

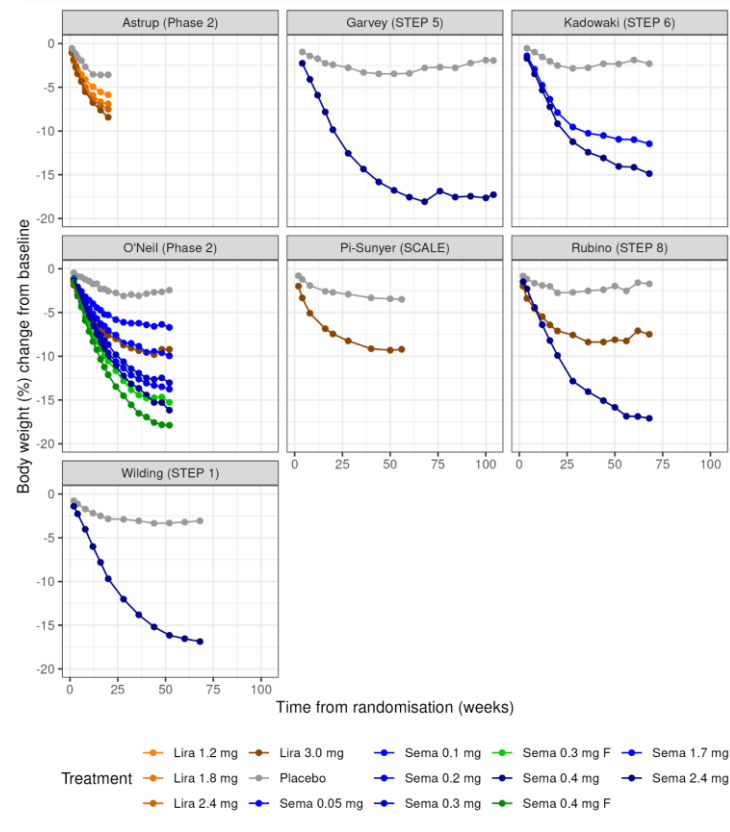
$$\boldsymbol{\gamma}_i \sim N(\mathbf{0}, \boldsymbol{\Omega} \otimes \mathbf{T}_i)$$

- Where $\boldsymbol{\Omega}$ is an unstructured covariance matrix ($n_p \times n_p$) for parameters, \mathbf{T}_i is the known covariance matrix ($n_i - 1$ by $n_i - 1$) with 1 on the diagonal elements and 1/2 on the off-diagonal elements, accounting for correlated random effects in multi-arm studies
- The model is fitted in a Bayesian framework, with model selection suggested by the expected log posterior density (ELPD) criterion

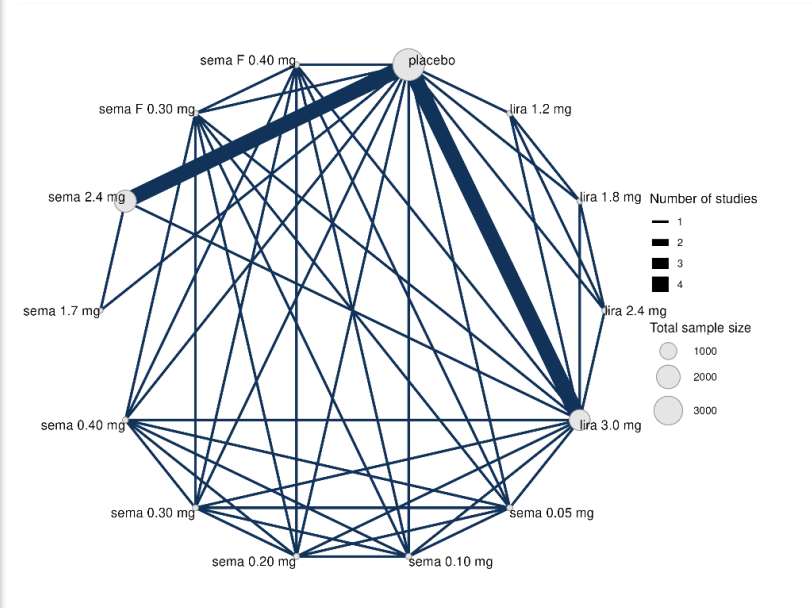
Application of DT-MBNMA to a network of obesity trials

An (Illustrative) Application to an Evidence Network of Obesity Trials

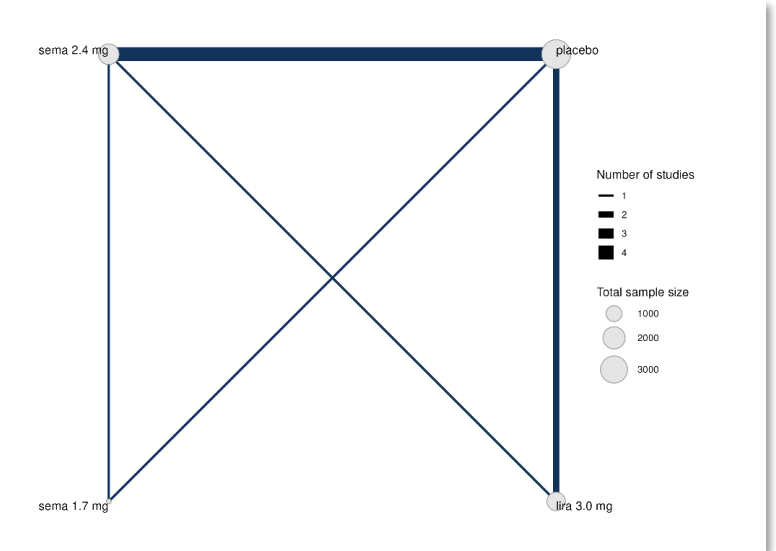
Raw Data



“Complete” Network

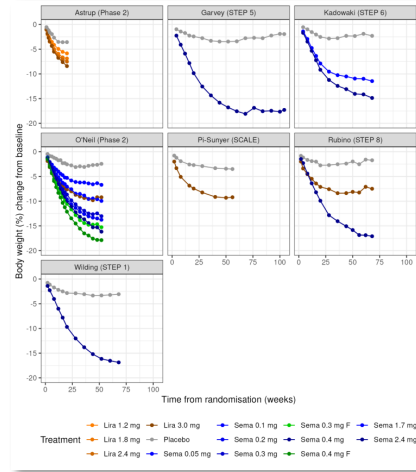


“Reimbursement” Network



Model Fitting

Data: Observed data for illustration purposes



- Models:
 - Time-course models (T-MBNMA), treating each dose-and-treatment as independent
 - Dose-response time-course models (DT-MBNMA), assuming exponential time-course
 - Standard NMA (using only week 68 data)
- Target: EmaxT contrasts for T-MBNMA and DT-MBNMA; week 68 treatment contrast for NMA
- Model fit and selection guided by: ELPD, consistency checks (UME), between study SD, and posterior predictive checks

TABLE 4. Model fit statistics for time-course models, fitted to the obesity dataset.

Function	Treatment Effect	Within-arm correlation	ELPD	SE	Δ ELPD	SE(Δ ELPD)
Exponential	Exchangeable	AR-1	-97.4	11.2	0	0
Emax	Exchangeable	AR-1	-116	13.1	-19.1	4.39
Emax	Exchangeable	Independent	-202	31.4	-105	26.5
Emax	Common	Independent	-216	31.4	-119	26.8
Exponential	Exchangeable	Independent	-257	42.2	-160	40.7
Exponential	Common	Independent	-273	43.2	-176	41.9
Bateman	Common	Independent	-280	43.3	-182	42.1

ELPD: Expected Log Posterior Density Estimate

TABLE 5. Model fit statistics for dose-response time-course models, fitted to the obesity dataset.

EmaxT ^a	kT ^a	ELPD	SE	Δ ELPD	SE(Δ ELPD)	Between study SD (EmaxT)	Between study SD (kT)	Correlation (EmaxT, kT)	Within-arm correlation
Linear	Linear	-97	11	0	0	1.2 [0.49; 2.1]	0.18 [0.039; 0.34]	0.026 [-0.90; 0.77]	0.86 [0.71; 0.95]
Log-linear	Log-linear	-97	11	-0.56	1.5	0.73 [0.073; 1.6]	0.18 [0.065; 0.33]	-0.011 [-0.92; 0.87]	0.84 [0.68; 0.95]
Treatment level	Treatment level	-97	11	-0.59	1.4	0.73 [0.038; 2.1]	0.17 [0.0052; 0.58]	0.049 [-0.95; 0.96]	0.86 [0.71; 0.96]
UME	UME	-97	11	-0.62	1.4	0.74 [0.041; 2.1]	0.16 [0.0053; 0.56]	0.069 [-0.94; 0.96]	0.86 [0.71; 0.95]
Emax	Log-linear	-98	11	-0.72	1.3	0.74 [0.075; 1.6]	0.18 [0.057; 0.32]	-0.15 [-0.94; 0.79]	0.85 [0.68; 0.95]

^aThe exponential function $E_{max}T(1 - \exp(-\exp(kT) \times time))$ is specified for the time-course relationship

ELPD: Expected Log Posterior Density Estimate

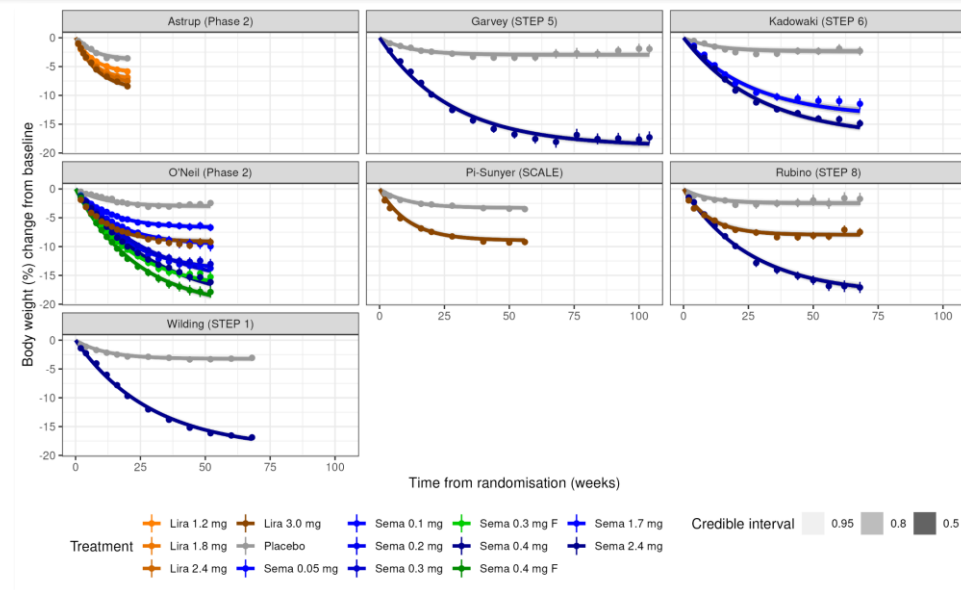
SE: Standard Error

UME: Unrelated means model

Treatment Contrasts

Comparison/Parameter	DT-MBNMA (Observed) ^{e,f}	DT-MBNMA (AR-1) ^{e,f}	T-MBNMA (AR-1) ^{e,f}	NMA	Direct Evidence
	EmaxT	EmaxT	EmaxT	Week 68	
Sema 1.7 vs Lira 3.0	-7.0 [-8.1, -6.0]	-6.8 [-8.0, -5.4]	-5.1 [-8.0, -2.6]	-4.4 [-7.78, -1.27]	—
Sema 1.7 vs Sema 2.4	2.9 [2.7, 3.1]	3.3 [2.5, 4.1]	5.4 [2.7, 7.7]	4.1 [1.3, 7.1]	3.7 [no CI] ^{a,c}
Sema 2.4 vs Lira 3.0	-10.0 [-11.1, -8.8]	-10.1 [-11.3, -8.9]	-10.4 [-12.0, -8.9]	-8.5 [-10.8, -6.5]	-9.4 [-12.0, -6.8] ^{a,d} -10.5 [-12.8, -8.1] ^{b,d}

Notes: ^a Treatment policy estimand; ^b Hypothetical estimand; ^c STEP 6 study; ^d STEP 8 study; ^e The exponential function $E_{max}T(1 - \exp(-\exp(kT) \times time))$ is specified for the time-course relationship; ^f EmaxT parameter contrast reported



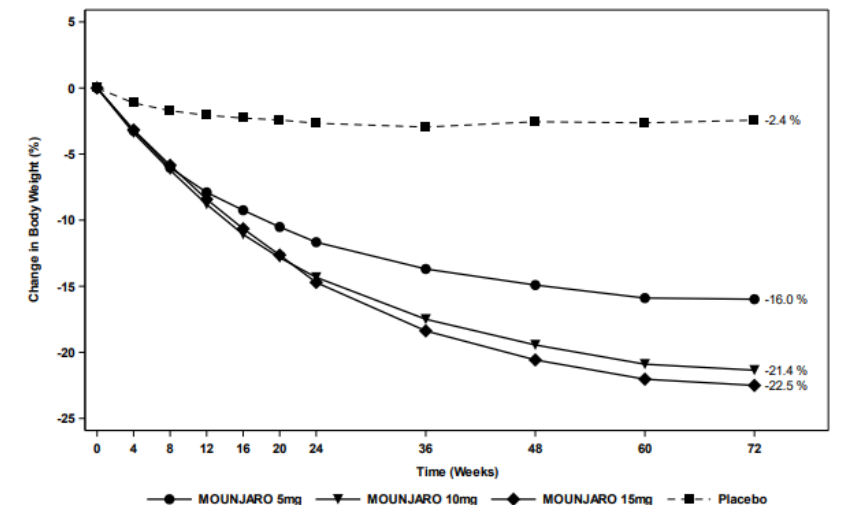
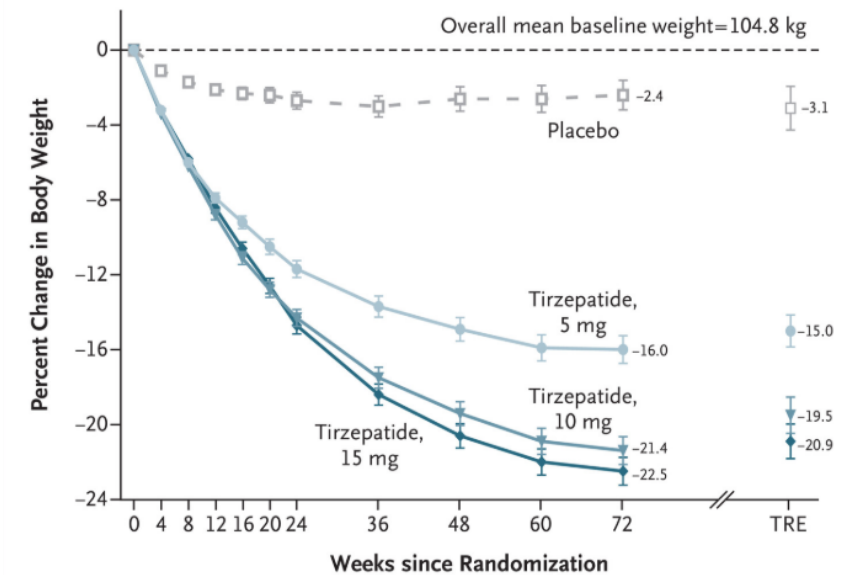
Summary

Summary

- We combine dose-response and time-course MB-NMA in a joint Bayesian framework
- Permits a richer use of evidence under additional parametric assumptions to answer questions of interest to support **portfolio decision making** and **HTA**:
 - Should we go H2H v this competitor?
 - How can we reduce uncertainty by using all available evidence in our HTA submission?
- Bayesian model-averaging may be an alternative to model selection
- Time-course data for competitor is often available from primary publications or HA documents

[Tirzepatide Once Weekly for the Treatment of Obesity | New England Journal of Medicine](#)
[Mounjaro, INN: tirzepatide](#)

B Percent Change in Body Weight by Week (efficacy estimand)



References

References

- Pedder H, Dias S, Bennetts M, Boucher M, Welton NJ. Joining the Dots: Linking Disconnected Networks of Evidence Using Dose-Response Model-Based Network Meta-Analysis. *Med Decis Making*. 2021;41(2):194-208.
- Pedder H, Dias S, Bennetts M, Boucher M, Welton NJ. Modelling time-course relationships with multiple treatments: Model-based network meta-analysis for continuous summary outcomes. *Res Synth Methods*. 2019;10(2):267-286.
- Mawdsley D, Bennetts M, Dias S, Boucher M, Welton NJ. Model-Based Network Meta-Analysis: A Framework for Evidence Synthesis of Clinical Trial Data. *CPT Pharmacometrics Syst Pharmacol*. 2016;5(8):393-401.
- Pedder H, Dias S, Boucher M, Bennetts M, Mawdsley D, Welton NJ. Methods to assess evidence consistency in dose-response model based network meta-analysis. *Stat Med*. 2022;41(4):625-644.
- Bergstrand M, Hooker AC, Wallin JE, Karlsson MO. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. *AAPS J*. 2011;13(2):143-151.
- Garrett ER. The Bateman function revisited: a critical reevaluation of the quantitative expressions to characterize concentrations in the one compartment body model as a function of time with first-order invasion and first-order elimination. *J Pharmacokinet Biopharm*. 1994;22(2):103-128.
- Brukner P-C. brms: An R package for Bayesian multilevel models using Stan. *Journal of statistical software*. 2017;80:1--28.
- Pedder H, Boucher M, Dias S, Bennetts M, Welton NJ. Performance of model-based network meta-analysis (MBNMA) of time-course relationships: A simulation study. *Res Synth Methods*. 2020;11(5):678-697.
- Gould AL. BMA-Mod: A Bayesian model averaging strategy for determining dose-response relationships in the presence of model uncertainty. *Biom J*. 2019;61(5):1141-1159.
- Strathe, Bøg, Gorst-Rasmussen: Model-based network meta-analysis: Joint estimation of dose-response and time-course relationships. *Under submission*

Appendix

Obesity Data

TABLE S4. Overview of the illustrative dataset

Agent	Author	Year	Study name	N	End of treatment	Treatments
Liraglutide	Astrup	2009	Phase 2 (1807) ^a	469	20	placebo, lira 1.2 mg, lira 1.8 mg, lira 2.4 mg, lira 3.0 mg
Liraglutide	Pi-Sunyer	2015	SCALE Obesity and Prediabetes	3731	56	placebo, lira 3.0 mg
Semaglutide	O'Neil	2018	Phase 2 (4153) ^b	957	52	placebo, sema 0.05 mg, sema 0.10 mg, sema 0.20 mg, sema 0.30 mg, sema 0.40 mg, sema 0.30 mg F, sema 0.40 mg F, lira 3.0 mg
Semaglutide	Wilding	2021	STEP 1	1961	68	placebo, sema 2.4 mg
Semaglutide	Garvey	2022	STEP 5	304	104	placebo, sema 2.4 mg
Semaglutide	Kadowaki	2022	STEP 6 ^c	302	68	placebo, sema 1.7 mg, sema 2.4 mg
Semaglutide	Rubino	2022	STEP 8	338	68	placebo, sema 2.4 mg, lira 3.0 mg

^aOrlistat treatment was excluded due to the inclusion criteria of comparing the effect of an GLP-1 to another GLP-1 or placebo (dietary restriction and adjunct to lifestyle intervention) for weight reduction in patients with obesity without diabetes.

^bSemaglutide dose levels were standardized to weekly equivalents by multiplying daily doses with 7 to match the once-weekly doses used in phase 3. The treatment labelled "F" represents doses, where semaglutide was dose-escalated in every second to target doses 0.30 mg and 0.40 mg, respectively.

^cSTEP 6 trial population included both normo-glycaemic, prediabetic and T2D subjects. To align with the study selection the T2D subgroup was excluded from the analysis and hence N=302.