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The role of modelling/simulation in paediatric population

A Practical Example: SGLT-2 Inhibitor and Type 2 Diabetes

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Outline

Example: SGLT2 inhibitor for type II diabetes

- **Background and Mechanism of Action**
- **Partial Extrapolation Approach including Modelling & Simulation**
- **Conclusions**

Paediatric Development Programme

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Agreed PIP:

PK/PD study and SE study in children 10 to 18 years

-> **Problem:** poor recruitment due to rarity & competing simultaneous paediatric developments for other new T2D drugs

Question:

Can an **Extrapolation Framework with Modelling & Simulation** help to design a more feasible study (objective: sample size/treatment effect)?

New PIP Proposal:

Changes to the T2DM paediatric programme utilising an **Extrapolation Framework with Modelling & Simulation**

for the SE study (reduced sample size)

Mechanism of Action

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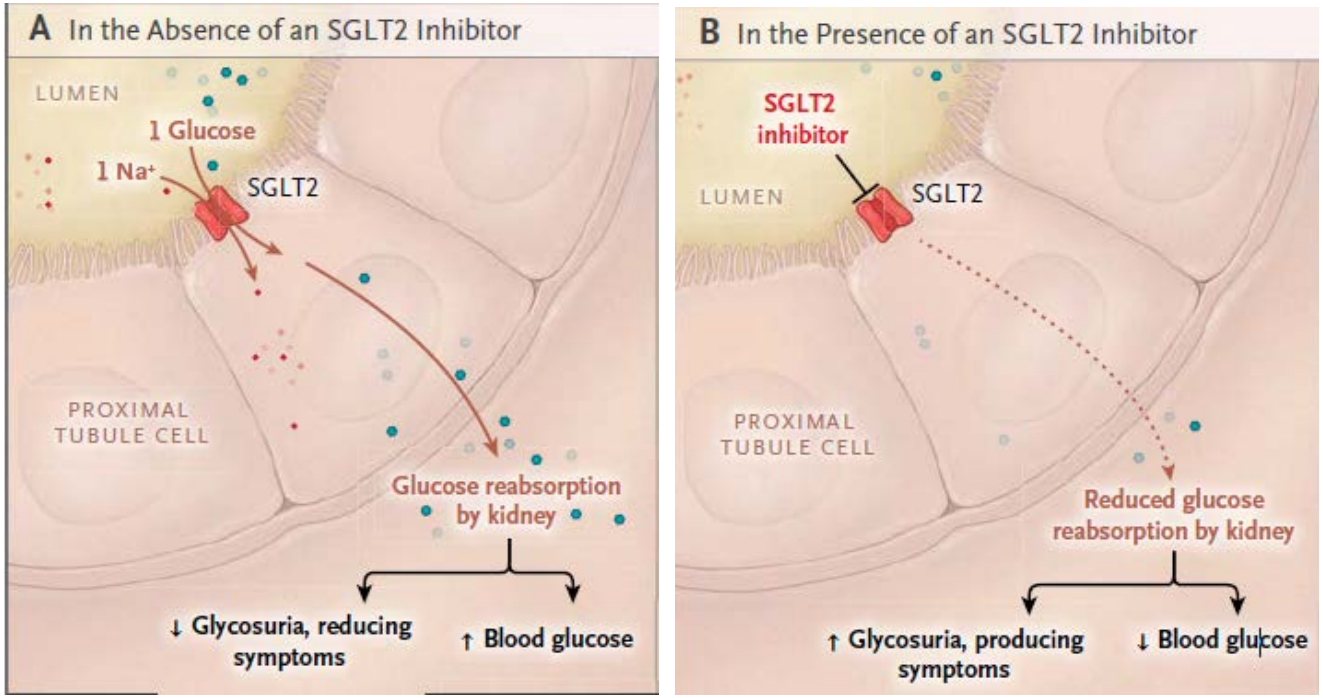
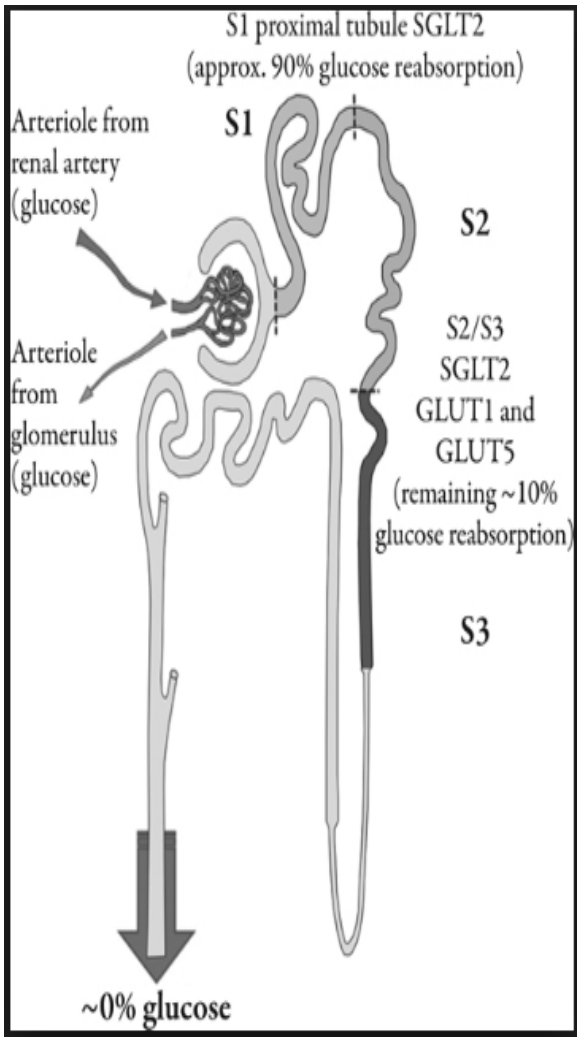


renal proximal tubule cells



Images taken from:

Type 2 Diabetes, SGLT2 Inhibitors, and Glucose Secretion; Hattersley AT, Thorens B. N Engl J Med. 2015 Sep 3;373(10):974-6. doi: 10.1056/NEJMcibr1506573.

Similarity / Difference of Disease in Adults vs Children

Main difference:

- Faster pace of beta-cell deterioration in children.
- Onset of disease more often acute (even with ketoacidosis and/or difficulties in weaning patients from insulin).
- T2D patients are still developing (pubertal-, bone- and neurocognitive development).

Target organ / molecule developmental differences?

Kidney function:

Mature latest by 2 years of age. However, adolescents with T2D may be expected to have better renal function than adults with T2D.

SGLT-2 maturation:

Expression levels of SGLT-2 similar in both population?

Studies included to integrate adult data in model-based meta-analysis

Table 4 Ten Phase 2b/3 studies on dapagliflozin in adult T2DM patients included in model-based meta-analysis

Study # (Subjects randomised, N)	Phase /duration (weeks)	Dapagliflozin dose (mg)	Pre-trial treatment	Therapy other than dapagliflozin	How is therapy effect modeled	How is effect of additional therapy modeled
MB102008 (N = 389)	2b /12	Monotherapy, 2.5, 5, 10, 20, 50	Naïve; Diet & exercise	Metformin alone (1500 mg) arm	Dapagliflozin as monotherapy; metformin as monotherapy	-
D1692C00005 (N = 279)	2b /12	Monotherapy, 1, 2.5, 5, 10	Naïve; Diet & exercise	-	Dapagliflozin as monotherapy	-
MB102013 (N = 558)	3 /24+	Monotherapy, 2.5, 5, 10, QAM & QPM	Naïve; Diet & exercise	-	Dapagliflozin as monotherapy	-
MB102032 (N = 282)	3 /24	Monotherapy, 1, 2.5, 5	Naïve; Diet & exercise	-	Dapagliflozin as monotherapy	-
MB102014 (N = 546)	3 /24+	Add-on, 2.5, 5, 10	Metformin	Metformin (~1500 mg)	Dapagliflozin as monotherapy	Metformin effect lumped into intrinsic Kin /kout
D1690C00006 (N = 808)	3 /24+	Add-on, 2.5, 5, 10	Insulin (>= 30 IU)	Insulin (>= 30 IU)	Dapagliflozin as monotherapy	Insulin effect lumped into intrinsic Kin /kout
MB102021 (N = 598)	3 /24	Monotherapy and initial combination with met, 5	Naïve; Diet & exercise	Metformin (start at 500 mg, titrate to 2000 mg)	Dapagliflozin as monotherapy; metformin as monotherapy; dapagliflozin+ metformin combination	-
MB102034 (N = 638)	3 /24	Monotherapy and initial combination with met, 10	Naïve; Diet & exercise	Metformin (start at 500 mg, titrate to 2000 mg)	Dapagliflozin as monotherapy; metformin as monotherapy; dapagliflozin+ metformin combination	-
D1690C00012 (N = 182)	3 /24+	Add-on, 10	Metformin	Metformin (≥1500 mg)	Dapagliflozin+ metformin combination	Metformin effect lumped into intrinsic Kin /kout
MB102029 (N = 252)	2 /3 /24+	Add-on, 5, 10	Various	Various	Dapagliflozin as monotherapy	Concomitant effect lumped into intrinsic Kin /kout

Paediatric data: helping the clinical trial simulation in paediatric patients with T2D

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Study 1 (CV138059)

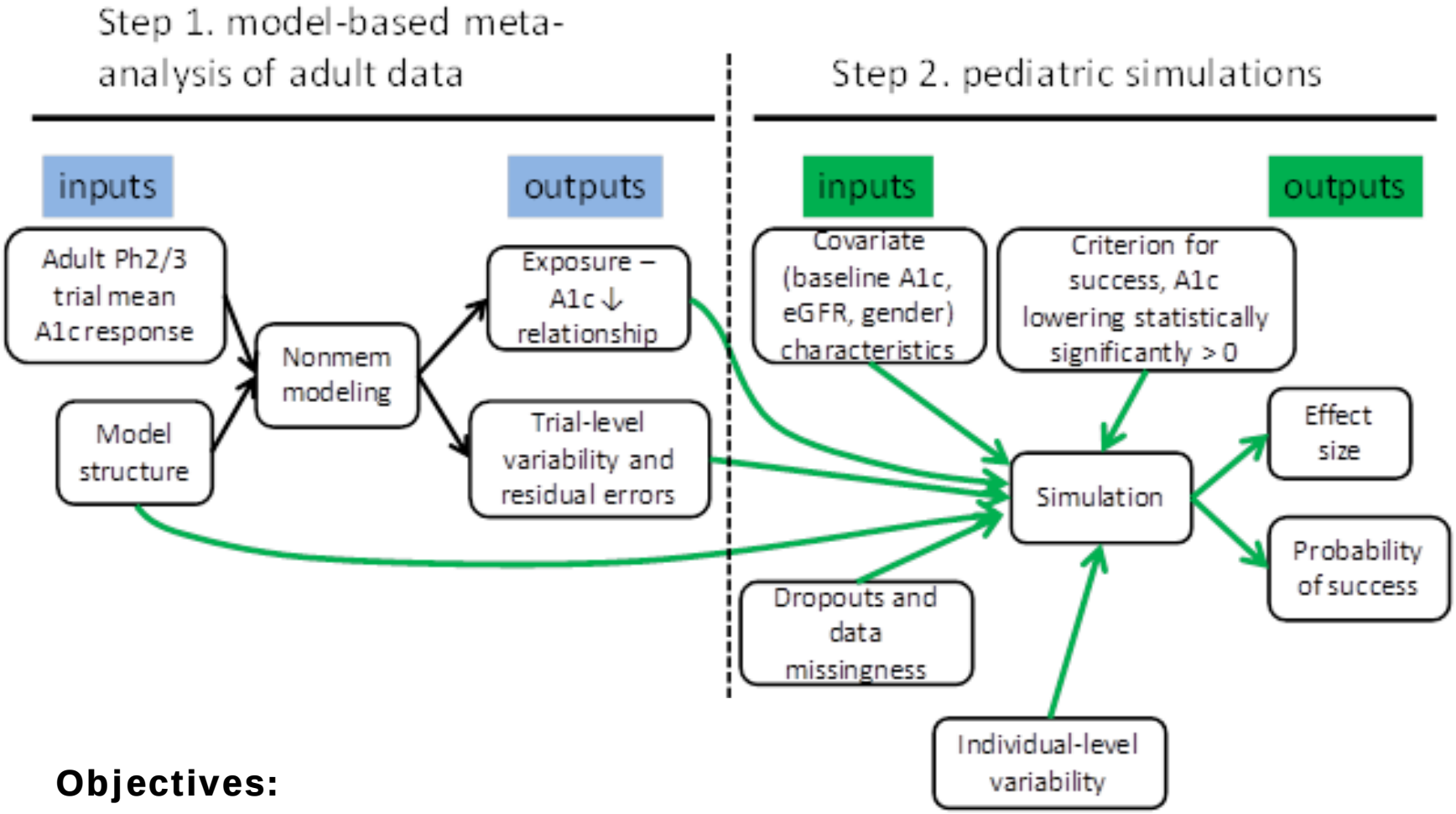
Double-blind, placebo-controlled, randomized study to investigate safety and efficacy of ***GLUCOVANCE*** (Metformin/Glyburide) vs Metformin and Glyburide Monotherapies in children and adolescents from 9 to less than 17 years with Type 2 Diabetes Mellitus (N=174).

Study 2 (AC2993-GWBQ)

Double-blind, placebo-controlled, randomized study to investigate safety and efficacy of ***exenatide*** twice daily (as monotherapy and adjunctive therapy to oral antidiabetic agents) in children and adolescents from 10 to less than 18 years with Type 2 Diabetes Mellitus (N=97).

259 subjects with records of eGFR, sex, and baseline HbA1c, which are covariates impacting the PK and exposure-HbA1c relationship of dapagliflozin. From these 259 subjects, a virtual patient population of 100000 was created via nonparametric bootstrapping with replacement in Splus.

SGLT2 inhibitor for type II diabetes



Objectives:

- Sample size calculation/treatment effect
- When data from SE study in children is available, validation of the model-based extrapolation of efficacy from adult to the paediatric population

Extrapolation framework

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Two steps

1. model-based meta-analysis integrating prior data and knowledge in the adults
    - indirect response model that links HbA1c response with steady-state daily plasma exposure or area under the curve (AUC_{ss}) of dapagliflozin based on the previously established Pop PK model and exposure-efficacy model
    - steady-state daily plasma AUC calculated as the ratio of dose over apparent clearance using gender and renal function as covariates
    - inhibition of HbA1c production according to an E_{max} function
    - baseline HbA1c, estimated glomerular filtration rate (eGFR) and study incorporated as covariates on PD parameters based on previous exposure-response understanding in adult patients.
2. clinical trial simulations in paediatric patients
    - using the adult model with parameter posteriors
        - predicting effect sizes of HbA1c lowering and probabilities of success
    - simulated dosing regimens included placebo, 5 mg, and 10 mg
    - baseline characteristics (HbA1c, eGFR, and sex) sampled from two previous paediatric trials

Key Assumptions

- The core exposure-HbA1c relationship, removed of all covariate effects, for dapagliflozin in paediatric patients is the same as in the adult patients;
- The rate constant for HbA1c clearance in paediatric patients is the same as in the adult patients;
- The HbA1c levels maintain steady state (i.e, the synthesis rate is approximately balanced by the clearance rate) prior to a trial in both adult and paediatric patients;
- The covariate effects on the PD parameters in paediatric patients are the same as in the adult patients;
- The potential impact of background therapies (exercise, diet, metformin, insulin, and combinations thereof) on the PD parameters, covariate effects, and HbA1c kinetics in paediatric patients is the same as in the adult patients;
- The individual level of variability in HbA1c lowering from baseline in paediatric patients is the same as in the adult patients;
- The data missingness and residual errors in paediatrics trials are the same as in the adult trials.

Predicted Mean Dose-HbA1c Response Relationship

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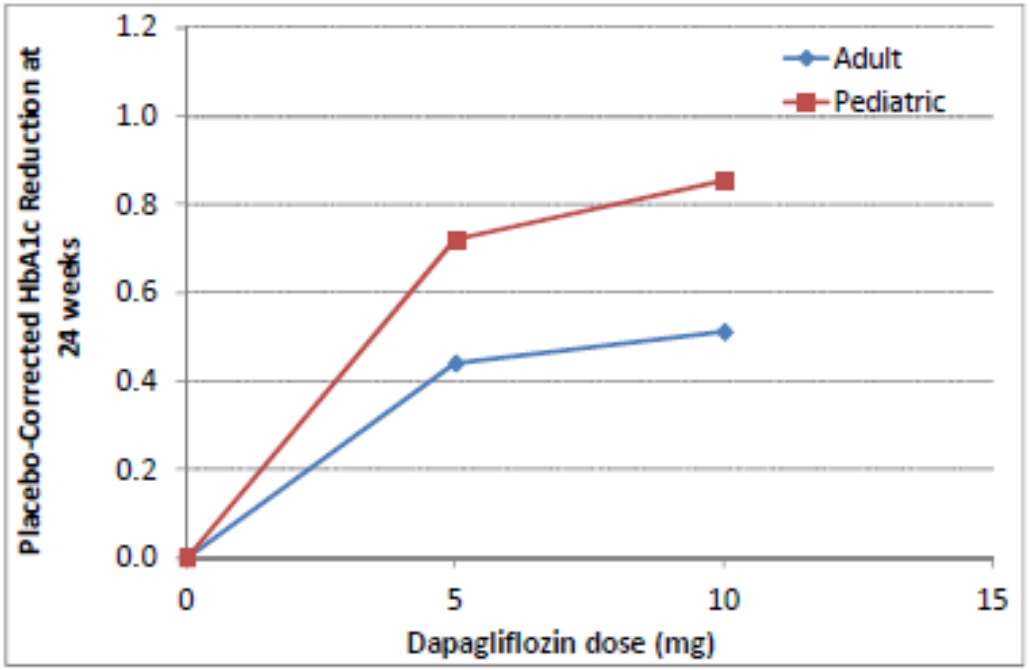
Figure 5.2.2-1: Predicted Mean Dose-HbA1c Response Relationship in Adult and Pediatric T2DM Patients Treated with Dapagliflozin Once Daily after 24 Weeks



Note: Mean dose-HbA1c response relationships derived under conditions: baseline HbAlc of 8% in both populations, and eGFR = 90 mL/min/1.73m^2 in adults and 120 mL/min/1.73m^2 in pediatric patients. The separation of the two dose-response curves is due to the difference in eGFR between the two populations.

Predicted Treatment Effect in Paediatric Patients is Significantly Higher in Adolescents

(better renal function!)

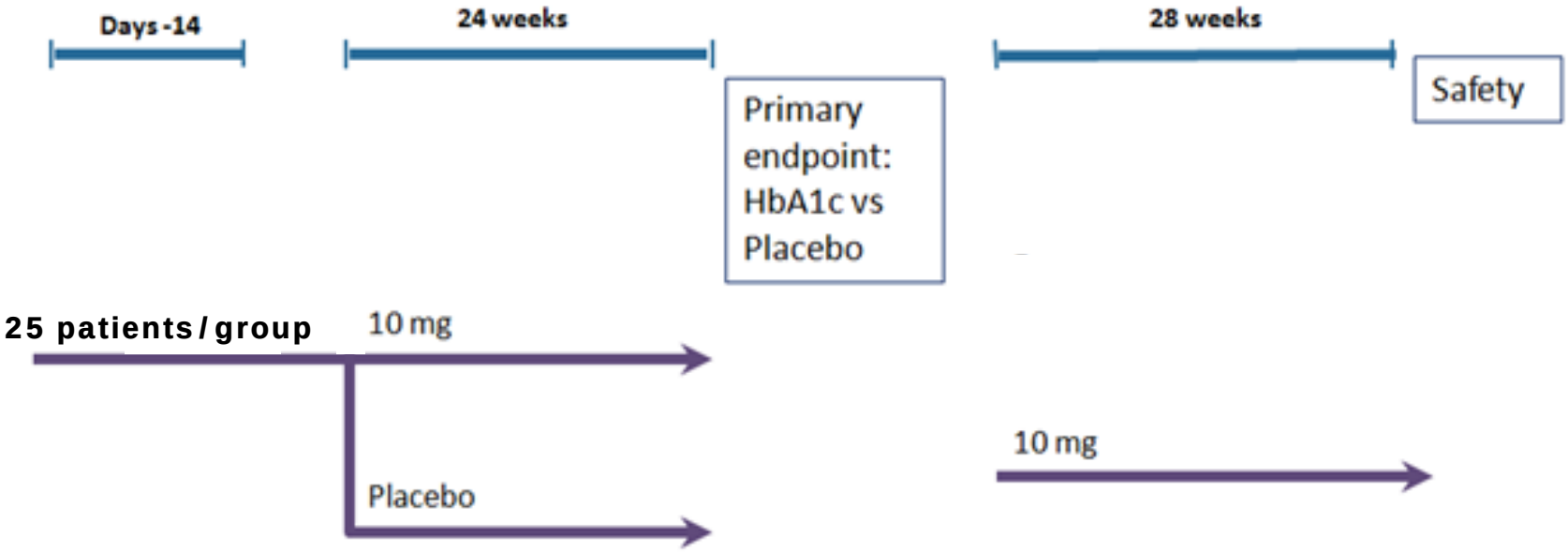
Dose: PK/PD Data in Adolescents

Table 1. PK parameters for Paediatric MB102091 and Adult MB102025 & MB102003 studies

		PK				24 h Urine Glucose (g)			
Study	Dose (mg)	n	Cmax (ng/ml) Geo mean (%CV)	AUC24 (ng/ml*h) Geo mean (%CV)	Tmax (h) Median (min, max)	n	Mean	SD	min, max
MB102091	2.5	7	24.75 (34.37)	91.42 (23.55)	1.50 (0.75, 2.00)	5	53.3	27.45	15.89, 91.66
	5	8	48.42 (40.59)	186.32 (27.51)	0.96 (0.58, 1.53)	8	63	26.8	28.15, 94.37
	10	8	117.84 (35.26)	416.75 (31.16)	0.875 (0.75, 4.00)	7	89.8	41.63	52.17, 177.31
MB102025	2.5	9	43 (30)	123 (29)	0.5 (0.5, 1.00)		37.9	12.81	18.29, 57.2
MB102003	5	11	66 (37)	220 (32)	1.00 (0.50, 2.00)		45.2	44.92	2.44, 170.2
MB102025	10	9	188 (27)	602 (23)	1.00 (0.5, 1.00)		68.4	13.44	49.08, 95.02

- 10 mg chosen as optimal dose for confirmatory paediatric study, as per simulations, **expected higher efficacy in adolescents**.
  Large safety margins (as seen in adults: single doses of up to 500 mg being well tolerated in healthy adults).

New Study Proposal: Reduced Sample Size



Objective: Reduction in sample size from 70 to **25** evaluable patients per group.

-> As per Simulation: this would give an **85%** probability of demonstrating superiority to placebo for the 10 mg dose with a placebo-corrected **HbA1c lowering at 24 weeks of -0.78%** (90% CI -0.28%, -1.26%), an overall alpha at **0.05** and with assuming a standard deviation of **0.9%**.

Optimizing trial design of pediatric study re. statistical analysis

- choice between different procedures to account for multiplicity w.r.t. to multiple doses
  - Dunnet
  - Hochberg
  - Hierarchical testing
- longitudinal analysis (mixed model for repeated measures) vs univariate analysis
- inclusion of covariates (baseline Hb1Ac)
- different imputation methods for missing data

Compare different trial designs and analysis methods using

- assumptions (distributions) based on the results of the extrapolation exercise
- using simulations to facilitate power and type 1 error calculations

Remaining Risks and Uncertainties

- Are all key assumptions reasonable (e.g. exposure-HbA1c realtionship)?

- Are SGLT2 density and adaptive renal changes similar in adults and children?

- Would the 5mg dose instead of the 10mg dose been the better choice?

- Given the small sample size and some remaining biological uncertainty, what is the risk of the study being underpowered?

- Long-term safety.

Conclusions

- **PK/PD modelling informed the effect size- pharmacometrics and biostatistics working together!**
- M&S at planning phase is a powerful tool for study optimisation.
- It is important to validate the extrapolation concept with actual paediatric clinical data.
- It is important to understand the uncertainties that the paediatric development needs to address.
- The planned paediatric phase 3 study will be the pivotal clinical evidence and at the same time allow validation of the extrapolation assumptions.

Thank you!