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A Mechanistic Model for the Effects of a Novel Drug on Glucose, Glucagon and Insulin Applied to Adaptive Phase II Design

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Background/Objectives

- A novel compound (MK) was developed for the treatment of Type 2 diabetes (T2D)
- A mechanistic model was developed to describe MK pharmacokinetics and glucagon, insulin and glucose profiles in healthy subjects during a glucagon challenge
- The model was adapted for the T2D patient population to assess the need for dose adjustment at the interim analysis of a Phase IIa study

Methods

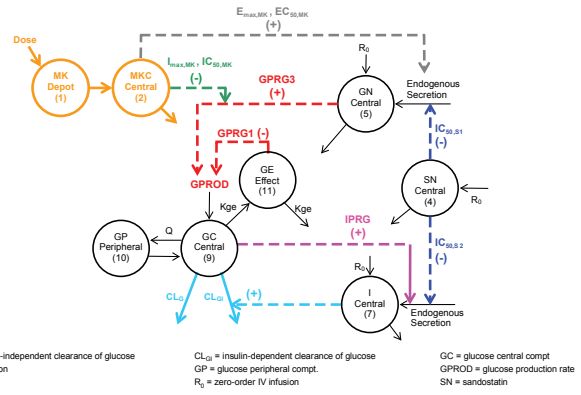
- Single oral doses of MK (0-900 mg) were given to 36 healthy subjects in a Phase I study (Table 1)
  - Starting from 3, 12 or 24 hr post dose, glucagon, sandostatin and basal insulin were infused for 2 hrs (glucagon challenge)
- A published model [1] was expanded incorporating drug, glucagon and sandostatin, as shown in Figure 1

Table 1. Study Design (Glucagon Challenge in Healthy Subjects)

Study# (N=36)	MK Dose (mg)&	MK Dose Clock Time	Infusion* Start Time Post MK Dose (h)	Infusion* Start Clock Time
PN001 part II (N=12)	0	8 am	3	11am
	100	8 am	3	11am
	300	8 am	3	11am
	900	8 am	3	11am
PN001 part III (N=12)	0	8 pm	12	8am
	10	8 pm	12	8am
	30	8 pm	12	8am
	100	8 pm	12	8am
	600	8 pm	12	8am
PN001 part IV (N=12)	0	8 pm	12	8am
	1	8 pm	12	8am
	3	8 pm	12	8am
	20	8 am	24	8am
	40	8 am	24	8am

Crossover with a balanced incomplete block design.
& A single oral MK dose was given.
* Glucagon, sandostatin and insulin were infused for 2 hrs. Sandostatin was given to inhibit endogenous glucagon and insulin secretions. Insulin was given to provide a low basal level of insulin to reduce the degree of excessive glycemia.

Figure 1. PK/Glucagon/Glucose/Insulin Model in Healthy Subjects with Glucagon Challenge



- Model key assumptions/descriptions are as follows
  - Glucose production rate (GPROD) was modulated by glucose and glucagon levels (**Equation 1**). Note: the effect of insulin on glucose production rate was implicit and covered by the glucose and glucagon effects
  - The effects of glucose and glucagon on GPROD were independent of each other (**Equation 1**)
  - At steady state, glucose and glucagon levels (Gss and GNss) were constant and therefore, GPROD was constant (homeostasis). When there were perturbations, increased glucose levels reduced GPROD, while increased glucagon levels increased GPROD (**Equation 1**)
  - The ability of glucagon to increase GPROD was reduced by MK exposure (Imax and IC50). When MK conc. was high enough, the ability of glucagon to increase GPROD was almost completely abolished (*i.e.*, Imax = 0.964) (**Equation 1**)
  - Clearance of glucose had two pathways: one was insulin-dependent (CLgi x CI) and the other was insulin-independent (CLg). The higher the insulin conc. (CI), the great the insulin-dependent clearance pathway of glucose (**Equation 3**)
  - Insulin endogenous secretion was regulated in a glucose-conc. dependent manner. When the glucose level increased above its steady-state conc. (Gss), insulin endogenous secretion increased. When the glucose level decreased below Gss, insulin endogenous secretion decreased (**Equation 4**)
  - MK increased glucagon secretion (Emax and EC50) (**Equation 5**)
  - Sandostatin inhibited glucagon and insulin secretions (Imax's and IC50s) (**Equations 4 & 5**)

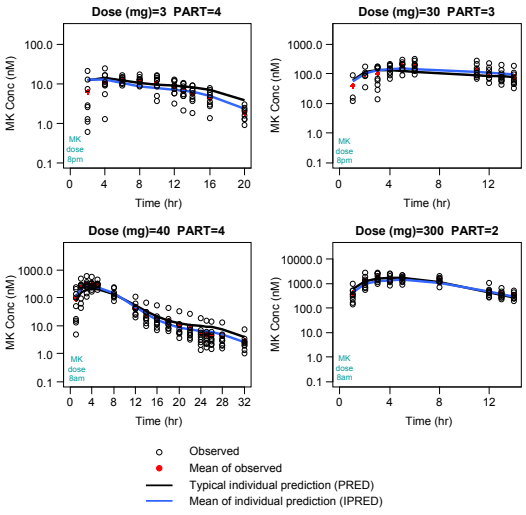
Equation #	Equation	Note
1	$GPROD = 0.5 * GPROD0 * \left(\frac{GE}{G_{SS}}\right)^{GPRG1} + \left(1 - \frac{I_{max,MK} * C_{MK}}{IC_{50,MK} + C_{MK}}\right) * \left(\frac{GN_{normal}}{GN_{ss}}\right)^{GPRG3}$ (Glucose production rate; Steady state production rate; Glucose negative feedback on its own production (GPRG1<0); MK reduces the potency of the glucagon effect; Glucagon stimulates glucose production (GPRG3>0))	Glucose production
2	$GPROD0 = G_{SS} * (CL_G + CL_{GI} * I_{SS})$ (Steady state production rate; Insulin-independent clearance of glucose; Insulin-dependent clearance of glucose)	Glucose production
3	$\frac{dA(9)}{dt} = GPROD + K_{PG} * A(10) - (K_{GP} + K_G + K_{GI} * C_I) * A(9)$ (The rate of change of glucose amt in the central compt; Glucose prod. rate; Distribution b/w the central & peripheral compt.'s; Insulin independent clearance; Insulin dependent clearance)	Glucose
4	$\frac{dA(7)}{dt} = I_{ss} * CL_I * \left(\frac{CGC}{G_{ss}}\right)^{IPRG} * \left(1 - \frac{C_S}{IC_{50,S2} + C_S}\right) - k_I * A(7)$ (The rate of change of insulin amt in the central compt; Steady-state secretion rate; Glucose stimulates insulin secretion (IPRG>0); Sandostatin inhibits insulin secretion; Insulin elimination)	Insulin
5	$\frac{dA(5)}{dt} = GN_{ss} * CL_{GN} * \left(1 + \frac{E_{max,MK} * C_{MK}}{EC_{50,MK} + C_{MK}}\right) * \left(1 - \frac{C_S}{IC_{50,S1} + C_S}\right) - k_{GN} * A(5)$ (The rate of change of glucagon amt in the central compt; Steady-state secretion rate; MK stimulates glucagon secretion; Sandostatin inhibits glucagon secretion; Glucagon elimination)	Glucagon

- The model was then modified using steady-state analysis for patients accounting for differences in the PD parameters between healthy subjects and T2D patients
- Clinical trial simulations (CTS) were subsequently performed to extrapolate drug effects to T2D patients in a Phase IIa study setting where no glucagon challenge was given
- NONMEM and R were used for modeling and NONMEM and SAS were used for CTS

Results

- Examples of MK pharmacokinetic profiles are shown in **Figure 2**

Figure 2. Examples of MK Pharmacokinetic Profiles



- The PD model parameter estimates are shown in **Table 2**
  - The drug effect was modeled by using an inhibitory Emax model (Imax=0.96 and IC50=13.7 nM) on the ability of glucagon to increase GPROD
  - In addition, an Emax model (Emax=0.79 and EC50=575 nM) to increase glucagon secretion by the drug was used to account for the increased glucagon concentrations pre-challenge (*via* compensatory feedback)

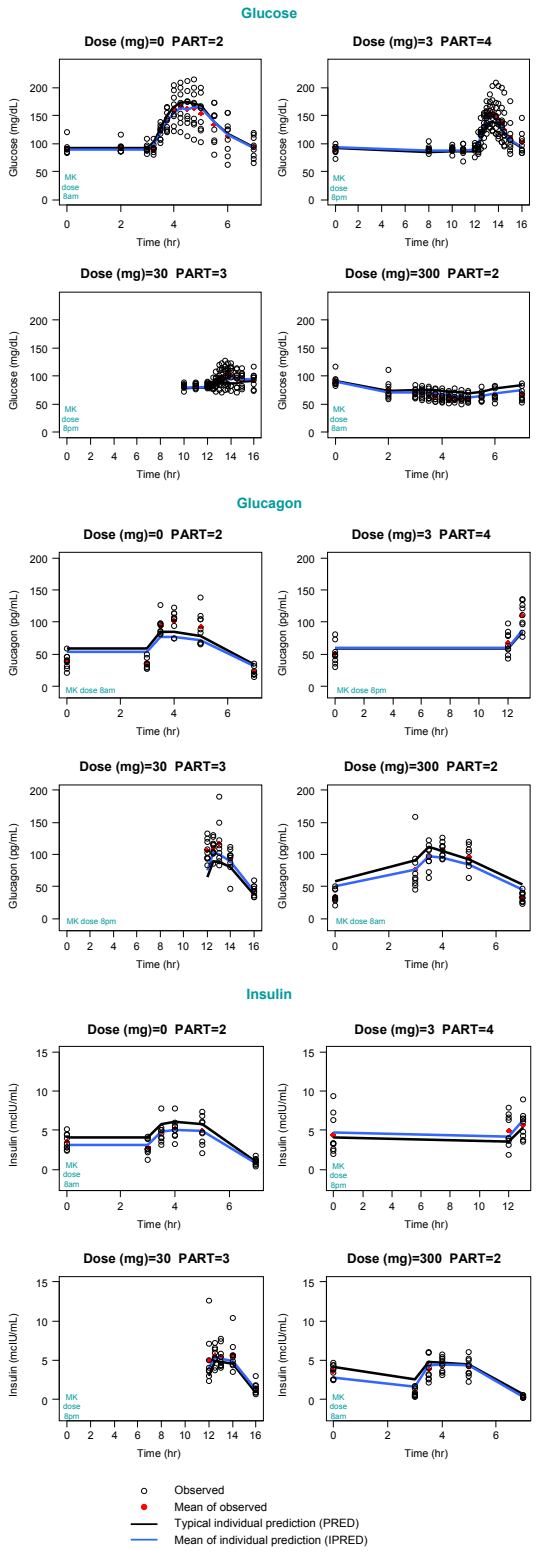
Table 2. Model Parameters for Glucose, Glucagon and Insulin in Healthy Subjects

Parameter (unit)	Description	Parameter Estimate	IIV (%CV)
Glucose			
GSS (mg/dL)	Glucose SS concentration	91.9	6.1 FIXED
CLG (dL/hr)	Glucose insulin-independent clearance	0.613	N.E.
CLGI (dL/hr/mcIU/mL)	Glucose insulin-dependent clearance	0.135	N.E.
QG (dL/hr)	Glucose intercompartmental clearance	0.269	N.E.
VGC (dL)	Glucose central compartment volume	1.13	28.8 FIXED
VGP (dL)	Glucose peripheral compartment volume	0.471	N.E.
KGE (1/hr)	Glucose ke0 for glucose regulation	0.0828	N.E.
Imax,MK	Imax of MKs inhibit effect on glucagon stimulation on glucose production	0.964	N.E.
IC50,MK (nM)	IC50 of MKs inhibit effect on glucagon stimulation on glucose production	13.7	78.2
GPRG1	Glucose negative feedback effect on glucose production	-2.16	N.E.
GPRG3	Glucagon stimulatory effect on glucose production	4.18	N.E.
RESG (%)	Glucose residual %CV	7.52	--
Insulin			
ISS (mcIU/mL)	Insulin SS concentration	4.13	33.3 FIXED
CLI (L/kg/hr)	Insulin clearance	1.4	26.3 FIXED
VI (L/kg)	Insulin volume	0.317	N.E.
IPRG	Glucose stimulation effect on insulin secretion	2.27	N.E.
IC50,S2 (ng/L)	Sandostatin IC50 on insulin secretion	0.944	N.E.
RESI (mcIU/mL)	Insulin residual SD	1.38	--
Glucagon			
GNSS (pg/mL)	Glucagon SS concentration	58.5	10.6 FIXED
CLGN (L/kg/hr)	Glucagon clearance	3.22	18.4 FIXED
VGN (L/kg)	Glucagon volume	1.44	N.E.
Emax,MK	Emax of MK's stimulatory effect on glucagon secretion	0.788 FIXED	N.E.
EC50,MK (nM)	EC50 of MK's stimulatory effect on glucagon secretion	575 FIXED	N.E.
IC50,S1 (ng/L)	Sandostatin IC50 on glucagon secretion	5.52	N.E.
RESGN (%)	Glucagon residual %CV	30.5	--

IIV = Inter-individual variability
N.E. = Not estimated
The model was minimized successfully. The covariance matrix was not estimated due to the very long running time.
The parameters in blue need to be interpreted with caution. Because a glucose dose was never given, the glucose volume of distribution could not be estimated. Another model with different parameterization which estimated KG, KGI, KGP and the ratio of VGP/VGC was explored. Despite different parameterization, both models show very similar fits for glucose, glucagon and insulin. Therefore, this model was used as the final model for simulations.

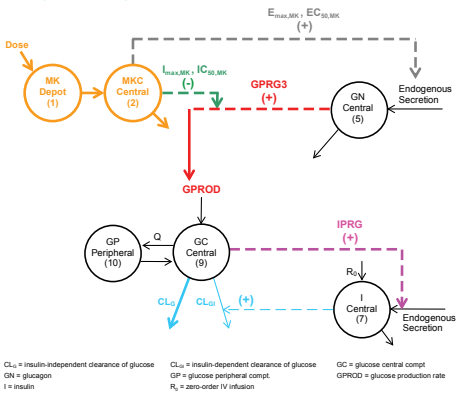
- The examples of model fits for glucose, glucagon and insulin pre- and post-challenge in healthy subjects are shown in **Figure 3**

Figure 3. Examples of Model Fits for Glucose, Glucagon and Insulin Pre- and Post-Challenge in Healthy Subjects



- This model was then extrapolated to T2D patients after accounting for differences in the PD parameters between healthy subjects and T2D patients (**Figure 4**)

Figure 4. PK/Glucagon/Glucose/Insulin Model in T2D without Glucagon Challenge



- To extrapolate to T2D
  - PK parameters: same between healthy and T2D
  - No glucagon challenge; only glucagon baseline conc. used in the model
  - Self-regulation of glucose production in T2D was completely compromised (note that this assumption is not completely physiological)
  - Baseline glucose level was 183.8 mg/dL for T2D vs. 91.9 mg/dL for healthy subjects (*i.e.*, doubled). There was interplay between the baseline levels of glucose, glucagon and insulin
  - Insulin-dependent clearance of glucose was estimated to be 11% in T2D compared to that in healthy subjects, based on the in-house data
  - Insulin-independent clearance/uptake of glucose is preserved
  - All other parameters were fixed based on estimates from the healthy subject model
- CTS was performed to estimate drug effects in T2D patients in a Phase IIa study setting
- Because the model PD output was fasting plasma glucose (FPG), but weighted mean glucose (WMG) was the PD endpoint for the Phase IIa study, a linear model between FPG and WMG was developed using the data from the Diabetes Control and Complications Trial [2]
- **Table 3** shows the parameter estimates and **Figure 5** shows the goodness-of-fit
- The same model structure to correlate WMG to FPG was used to fit the data from the lead compound in the same class in T2D, and yielded similar parameter estimates (results not shown)

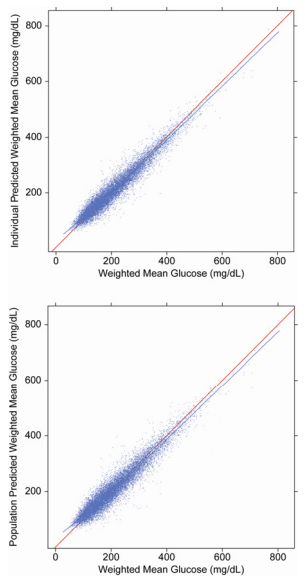
Table 3. Parameter Estimates for the Linear Model between FPG and WMG

wmg = a*[pre-breakfast] + b*[pre-lunch] + c*[pre-supper] + d*[bedtime] + intercept + η_{AN} + ε

Solution for Fixed Effects					
Effect	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept	21.979	0.461	26139	47.6	<.0001
Pre-breakfast	0.262	0.0018	26139	143.6	<.0001
Pre-lunch	0.190	0.0017	26139	110. 9	<.0001
Pre-supper	0.271	0.0016	26139	166.6	<.0001
Bedtime	0.238	0.0016	26139	151.0	<.0001
SD(η_{AN})	9.28				
SD(ε)	22.44				

All glucose concentrations were in mg/dL.

Figure 5. Goodness-of-Fit Plots for the Linear Model for WMG



Red line = line of unity. Blue curve = loess smoothed curve.

- **Table 4** shows the WMG simulation results with 1000 trials and 82 subjects/trial

Table 4. Weighted Mean Glucose Simulation Results

Dose, Time	MK Dose (mg)	Simulated LS-mean WMG decrease (mg/dL)	Dose Change*		
			Decrease	Keep	Increase
QD, AM	5	27.23	0	68.8	31.2
	6	30.26	0	89.1	10.9
	7	33.12	0.9	96	3.1
	8	35.04	2.6	96.9	0.5
	9	37.11	8.4	91.6	0
	10	39.35	20.5	79.5	0
	11	40.77	30.9	69.1	0
	12	42.37	44.2	55.8	0
	14	45.15	66.7	33.3	0
QD, PM	3	24.79	0	44.3	55.7
	4	29.32	0.1	82.7	17.2
	5	33.84	1.4	96.3	2.3
	6	37.04	8	91.6	0.4
	7	40.23	25.4	74.6	0
	8	42.95	49.5	50.5	0
	9	45.36	67.8	32.2	0
	10	47.57	83.9	16.1	0
	12	51.36	97	3	0
BID	13	73.06	-	100	0
	14	74.14	-	100	0
	16	76.57	-	100	0
	17	77.65	-	100	0
	18	78.66	-	100	0
	20	80.29	-	100	0
	22	81.73	-	100	0
	25	83.73	-	100	0
	30	85.77	-	100	0

* For QD doses, the dose rules were that if the 80% post-hoc prediction interval of the study mean reduction in WMG was <30 mg/dL, increase the dose, and if it was >40 mg/dL, decrease the dose. For BID there was only an increase rule if the 80% post-hoc prediction interval was <60 mg/dL.

- According to simulations,
  - The current doses (highlighted in green) were near optimal
  - The AM dose would likely be best adjusted to either 7 or 8 mg
  - The PM dose would likely be best adjusted to 5 mg, and
  - The BID dose would not require increase

Conclusions

- A PK/PD model was developed to adequately capture the interplay between glucose, glucagon and insulin in healthy subjects or T2D patients, with or without glucagon challenge
- A linear model to correlate FPG to WMG was developed and provided robust predictions to assist with the dose adjustment for the interim analysis

References:

[1] Silber HE, Jauslin PM, Frey N, Gieschke R, Simonsson USH, Karlsson MO. An integrated model for glucose and insulin regulation in healthy volunteers and Type 2 diabetic patients following intravenous glucose provocations. Journal of Clinical Pharmacology, 2007;47:1159-1171.

[2] The Diabetes Control and Complications Trial (DCCT) was a clinical study conducted from 1983 to 1993 funded by the National Institute of Diabetes and Digestive and Kidney Diseases with 1441 Type 1 diabetic patients treated with insulin.