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Hi. We're HumMod.
The best, most complete, mathematical model of human physiology ever created.

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- Completely customizable
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- Published in peer-reviewed literature

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Try » Conquer

QCP
HumMod's famous predecessor.
QCP

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Knowledge Base
This is our starting point for the collective knowledge of HumMod. New tutorials, information, etc. appears in the Knowledge Base first.
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Supporting Papers
Want to know what info we used to build the first version of HumMod? Well, here are the 5,000+ papers we used. They're catalogued in a reference database called Zotero.
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This figure provides an example of the ability of HumMod to simulate time dependent physiological responses. In this example the “person” is

- initially lying down for 10 min,
- then stands for 10 min,
- followed by 30 min of exercise.
This figure demonstrates the cardiac output and blood flow responses before and during the exercise period.
This figure demonstrates the skeletal metabolism responses before and during the exercise period.
This figure demonstrates the multilevel aspects of HumMod. This figure displays the renal distal tubule sodium responses before and during the exercise period.
HumMod Origin

1960's
Dr. Arthur Guyton starts mathematical analysis of integrative physiology (Millhorn and Guyton, 1965).
1970's

Over the next 10 years, Guyton and colleagues (1972) developed a model of cardiovascular physiology. Guyton used the 1972 model to test a variety of physiological hypotheses, mainly focusing on acute and chronic blood pressure control and the role of the kidney in the long term regulation of blood pressure.

1980's

In 1983, with the advent of the personal computer, Coleman and Randall developed a model of human physiology called Human (1983).
1990's

Human was expanded into a Windows software package called Quantitative Circulatory Physiology (QCP).

QCP was limited. All the physiological descriptions were written in C and compiled into an executable. But there was a way to make the physiology more accessible. With the help of Dr. Robert Hester, Dr. Coleman created...
2000's

HumMod – The best, most complete, mathematical model of human physiology ever created.
The XML code used to describe a curve function. \(X_m\) is an \(X\) value, \(Y_m\) is the associated \(Y\) value, and \(S_m\) is the slope of the curve at the \(X_m, Y_m\) data point. (B) This demonstrates how the curve function is called in the XML code. “Variable name” is the output value returned following evaluation of the curve function at a given input value. (C) Describes the relationship between blood glucose and insulin release. (D) Shows the sigmoid fit based on the \(X, Y,\) and slope data presented in (C).
The Entelos Hypertension PhysioLab® platform
- quantitatively models the human reno-cardiovascular system to predict responses to perturbations that lead to essential hypertension and chronic kidney disease
- models the effects of antihypertensive therapies on blood pressure control and secondary end organ damage endpoints, with a focus on the renin-angiotensin-aldosterone system (RAAS).
- the effects of RAAS-based antihypertensive therapies on long-term blood pressure control and renal function are explicitly represented in the platform.

The Hypertension PhysioLab platform is a dynamic model of cellular and molecular interactions that enables prediction of the following clinically-relevant phenomena over time:

- blood pressure regulation (mean arterial pressure, total peripheral resistance, cardiac output)
- glomerular filtration rate (glomerular conductance, hydrostatic and oncotic pressures)
- albuminuria (glomerular sieving and tubular reabsorption)
- systemic and intrarenal RAAS with glomerular and tubular components
- dynamics of renin, prorenin, plasma renin activity (PRA), Ang I, Ang II, and Ang 1-7 formation.
The Hypertension PhysioLab platform reproduces many of the physiological responses and underlying biological attributes of Hypertension in different patient types.

Individual virtual patients are explicitly represented mechanistically, and virtual populations comprising sets of virtual patients reproduce the means and variances for therapeutic responses in clinical trials.

These virtual patients exhibit:
- disease progression patterns that take into account pathophysiological diversity of hypertensive and diabetic subjects
- diverse baseline characteristics that correspond to inclusion criteria of patients recruited in clinical trials
The Hypertension PhysioLab platform is a powerful tool to evaluate the renoprotective performance of novel antihypertensive drugs against current standards of care by stratifying clinically relevant patients and being able to explore the effects of drugs on different clinical phenotypes.

Hypothesis testing of therapy responses can be conducted by using the platform's capability for simulation of the effects of non-RAAS and RAAS-based therapies.

Furthermore, single or combination therapies can be simulated to assess their renoprotective potential and support competitive differentiation strategies.
Rapidly evaluate the effect of hypertension compounds on cardio-renal endpoints before initiating lengthy trials

Our Hypertension PhysioLab® platform predicts the effects of therapies on renal function, blood pressure regulation, and renal disease progression

Diverse patient types:
- Normal renal function
- Essential hypertensive
  - Increased efferent arteriole resistance
- Essential hypertensive
  - Increased systemic vascular resistance
- Renal hypertensive
  - Increased sodium reabsorption in nephron
- Diabetic hypertensive
  - Glomerular damage, reduced GFR

Clinical outputs:
- Mean Arterial Pressure
- Glomerular Filtration Rate
- Albuminuria
- Plasma markers (PRA, Ang II, Aldosterone)

Relevant underlying biology:
- RAAS (renin-angiotensin-aldosterone system)
- Blood pressure regulation
- Vasoconstriction
- Tissue remodeling
- Renal hemodynamic regulation of Na+, water
- Disease effects on nephron (glomerular / tubular function)

Therapies currently represented in the Hypertension PhysioLab platform:
- ACE inhibitors
- Angiotensin receptor blockers
- Direct renin inhibitors
- Aldosterone antagonists
- Calcium channel blockers
- Beta blockers
- Thiazide diuretics
- Loop diuretics
## Summary of data used to calibrate the Hypertension PhysioLab Platform

### Short-term studies in hypertensive patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Phenotype / Disease</th>
<th>n</th>
<th>Duration</th>
<th>Drugs tested</th>
<th>Clinical endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erley, 1995</td>
<td>HT</td>
<td>9</td>
<td>1 mo</td>
<td>losartan, ramipril</td>
<td>v</td>
</tr>
<tr>
<td>Holdaas, 1998</td>
<td>HT / non diab nephrop.</td>
<td>9</td>
<td>1 mo</td>
<td>losartan, ramipril</td>
<td>v</td>
</tr>
<tr>
<td>Nussberger, 2007</td>
<td>HT</td>
<td>569</td>
<td>2 mo</td>
<td>aliskiren, irbesartan</td>
<td>v</td>
</tr>
<tr>
<td>Stanton, 2003</td>
<td>HT</td>
<td>226</td>
<td>1 mo</td>
<td>aliskiren</td>
<td>v</td>
</tr>
<tr>
<td>Nielsen, 1997</td>
<td>HT</td>
<td>15</td>
<td>1 mo</td>
<td>losartan, amlodipine</td>
<td>v</td>
</tr>
</tbody>
</table>

### Long-term progression and therapy in diabetic patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Phenotype / Disease</th>
<th>n</th>
<th>Duration</th>
<th>Drugs tested</th>
<th>Clinical endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelson, 1996</td>
<td>T2DM, Pima</td>
<td>194</td>
<td>4 yr</td>
<td>progression</td>
<td>v</td>
</tr>
<tr>
<td>Ravid, 1998</td>
<td>T2DM / early</td>
<td>156</td>
<td>6 yr</td>
<td>enalapril</td>
<td>v</td>
</tr>
<tr>
<td>IRMA2, 2001</td>
<td>T2DM, microalbumin</td>
<td>590</td>
<td>2 yr</td>
<td>irbesartan</td>
<td>v</td>
</tr>
<tr>
<td>DETAIL, 2004</td>
<td>T2DM / early nephrop.</td>
<td>250</td>
<td>5 yr</td>
<td>telmisartan, enalapril</td>
<td>v</td>
</tr>
</tbody>
</table>

© 2010 Entelos, Inc.
Summary of data used to validate the Hypertension PhysioLab Platform

<table>
<thead>
<tr>
<th>Study</th>
<th>Phenotype / Comorb.</th>
<th>n</th>
<th>Duration</th>
<th>Drugs tested</th>
<th>Clinical endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>RENAAL, 2001</td>
<td>T2DM / late nephrop.</td>
<td>1513</td>
<td>3.4 yr</td>
<td>losartan</td>
<td>✅ ✅</td>
</tr>
<tr>
<td>AVOID, 2008</td>
<td>T2DM / Nephrop.</td>
<td>599</td>
<td>6 mo</td>
<td>aliskiren, losartan</td>
<td>✅ ✅ ✅</td>
</tr>
</tbody>
</table>
PS15.7
Using a Systems Biology Approach to Explore Clinical Diversity and Explain Results from Clinical Trials: Example of the RAAS System in Hypertension

Schmidt, Henning
Novartis, Switzerland
Top-Down / Bottom-Up Approach
Connecting systems level output to intermediate physiological processes and further into mechanistic pathway level effectors of system dynamics

Clinical measurements of interest:
- MAP
- GFR
- Albuminuria
- UAER
- Platform output

Corresponding physiological behavior:
- Cardiac output
- Blood volume
- Glomerular pressure
- Renal oncotic pressure
- Glomerular membrane permeability

Underlying mechanistic network:
- Plasma renin activity, Ang II, Ang (1-7)
- Plasma glucose, aldosterone, ADH
- Renal Ang II, Ang (1-7), inflammatory mediators
- SNS activity, neural regulation, local regulation

MAP: mean arterial pressure
GFR: glomerular filtration rate
UAER: urinary albumin excretion rate
Biological pathways quantitatively represented in the systemic RAAS module

\[
PRA = \frac{V_{\text{max}}[\text{AGT}]}{[\text{AGT}]+[\text{AGT}]} \cdot f(\text{AT1-bound AngII})
\]

\[
\frac{d[\text{AGT}]}{dt} = k_{\text{AAG}} - PRA - \frac{\ln(2)}{h_{\text{AAG}}} [\text{AGT}]
\]

\[
\frac{d[\text{AngII}]}{dt} = PRA - (c_{\text{ACE}} + c_{\text{CPI}} + c_{\text{ATII}})[\text{AngII}] - \frac{\ln(2)}{h_{\text{ATII}}} [\text{AngII}]
\]

\[
\frac{d[\text{AngI}]}{dt} = c_{\text{ACE}} [\text{AngII}] + c_{\text{CPI}} [\text{AngII}] - c_{\text{ATII}} [\text{AngI}] - \frac{\ln(2)}{h_{\text{ATII}}} [\text{AngI}]
\]

\[
\frac{d[\text{AngIV}]}{dt} = c_{\text{ATII}} [\text{AngII}] - \frac{\ln(2)}{h_{\text{ATII}}} [\text{ATII-bound AngII}]
\]

\[
\frac{d[\text{AT2-bound AngII}]}{dt} = c_{\text{ATII}} [\text{AngII}] - \frac{\ln(2)}{h_{\text{ATII}}} [\text{AT2-bound AngII}]
\]

- Mechanisms with little or no data are estimated by mathematically solving for the equilibrium state in specific states (normal and hypertensive)
Results for a single normotensive virtual patient were derived from clinical measurements and model equilibrium solution.

<table>
<thead>
<tr>
<th>parameter</th>
<th>units</th>
<th>Normotensive VP</th>
<th>reported range</th>
<th>sample reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>[AGT]</td>
<td>pmol/ml</td>
<td>4.8</td>
<td>4.8-450000</td>
<td>Katsurada, 2007</td>
</tr>
<tr>
<td>[Ang I]</td>
<td>fmol/ml</td>
<td>7.5</td>
<td>4.8-450000</td>
<td>Nussberger, 2002</td>
</tr>
<tr>
<td>[Ang II]</td>
<td>fmol/ml</td>
<td>7.5</td>
<td>4.8-450000</td>
<td>Nussberger, 2002</td>
</tr>
<tr>
<td>[Ang (1-7)]</td>
<td>fmol/ml</td>
<td>4.75</td>
<td>2.2-7.3</td>
<td>Ferrario, 1990</td>
</tr>
<tr>
<td>AGT t½</td>
<td>hr</td>
<td>5</td>
<td>3.1-31.7</td>
<td>Hyp Primer</td>
</tr>
<tr>
<td>Ang I t½</td>
<td>min</td>
<td>25</td>
<td>16</td>
<td>Schalekarno, 1989</td>
</tr>
<tr>
<td>Ang II t½</td>
<td>min</td>
<td>0.5</td>
<td>0.5</td>
<td>Van Kalts, 1997</td>
</tr>
<tr>
<td>Ang (1-7) t½</td>
<td>min</td>
<td>0.5</td>
<td>0.5</td>
<td>Lisuf, 2008</td>
</tr>
<tr>
<td>Ang IV t½</td>
<td>min</td>
<td>29</td>
<td>29</td>
<td>estimated</td>
</tr>
<tr>
<td>PRA</td>
<td>ng/ml/hr</td>
<td>1.34</td>
<td>0.34-1.45</td>
<td>Nussberger, 2002</td>
</tr>
<tr>
<td>[Ang IV]</td>
<td>fmol/ml</td>
<td>0.84</td>
<td>?</td>
<td>solved</td>
</tr>
<tr>
<td>AGT synthesis rate</td>
<td>fmol/ml/hr</td>
<td>1.240</td>
<td>?</td>
<td>solved</td>
</tr>
<tr>
<td>NEP (Ang I-Ang (1-7))</td>
<td>1/hr</td>
<td>0.91</td>
<td>?</td>
<td>solved</td>
</tr>
<tr>
<td>ACE</td>
<td>1/hr</td>
<td>42.57</td>
<td>?</td>
<td>solved</td>
</tr>
<tr>
<td>chymase</td>
<td>1/hr</td>
<td>10.64</td>
<td>?</td>
<td>solved</td>
</tr>
<tr>
<td>ACE2</td>
<td>1/hr</td>
<td>0.074</td>
<td>?</td>
<td>assume</td>
</tr>
<tr>
<td>Ang II conversion to Ang IV</td>
<td>1/hr</td>
<td>0.74</td>
<td>?</td>
<td>solved</td>
</tr>
</tbody>
</table>
RAAS based therapies included in platform

- The appropriate nodes in the RAAS platform were calibrated to represent the effects of each therapy considered:
  1. ACE inhibitor (ACEI) – enalapril
  2. Direct Renin inhibitor (DRI) – aliskiren
  3. Angiotensin receptor blocker (ARB) – irbesartan

The therapeutic inhibitory effect of ACEI, ARB and DRI were implemented via the use of fractional reductions in enzyme activity, $\alpha$, $\beta$ and $\delta$, respectively.
Renal Module

- Nephron: basic functional unit of the kidney
- Glomerulus: that allows high filtration rates of fluid from the blood with unrestricted passage of small and mid-sized molecules, while restricting passage of serum albumin and proteins
- Tubular region: where filtered fluid is converted to urine via selective re-absorption and secretion
- Glomerular filtration rate (GFR): is the best estimate of kidney function
- Albuminuria: an early indicator and major risk factor for renal disease progression
- Objective: model GFR and albuminuria and predict response to RAS therapies using virtual patients that span clinical hypertensive and diabietic phenotypes
Renal Disease Progression Module

Modeling disease effects on the glomerular filtration rate (GFR)

- Disease Drivers
  - Albumin Sieving coefficient
  - Albumin excretion rate
  - Hydrostatic conductance

GFR

- No. of functional receptors

SNGFR

- Disease Drivers

albumin / creatinine ratio (UACR)

Disease Drivers: Glomerular Pressure, glucose, renal AngII, etc.
Renal module calibrated to reproduce renal disease progression observed in diabetes

- Patients with various duration of diabetes were followed for 4 years to assess progressive renal damage.
- Multiple biological hypotheses explored in model to reproduce the range of renal function observed in the diabetic state.
- Calibrating model to reproduce the diversity of behavior provided insights into the underlying physiology.
Virtual population development: overview

Every unique realization of full model parameters constitutes one Virtual Patient

Step 1: Identify mechanistic axes that influence clinical outcome

Step 2: Create candidate virtual patients by exploring parameters along axis within physiological range

Step 3: Check for consistency in virtual patient cohorts, eliminate non-physiological VPs

Use clinical data to determine criteria for phenotypic feasibility
Five mechanistic search axes selected to reflect basic hypertensive phenotypes for VP cohort creation

<table>
<thead>
<tr>
<th>Axis parameter(s)</th>
<th>Parameter variation (% from nominal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal tubule sodium reabsorption</td>
<td>63 – 113</td>
</tr>
<tr>
<td>Distal tubule sodium reabsorption</td>
<td>80 – 180</td>
</tr>
<tr>
<td>Total peripheral resistance</td>
<td>67 – 267</td>
</tr>
<tr>
<td>Preglomerular resistance scale**</td>
<td>50 – 500</td>
</tr>
<tr>
<td>Functional nephrons and Hydrostatic glomerular conductance</td>
<td>60 – 100 40 – 200</td>
</tr>
</tbody>
</table>


** - this is change in scale, actual changes in resistance are smaller.
Virtual patients were chosen based on criteria within the range of physiological feasibility.

<table>
<thead>
<tr>
<th>Measurement (at steady-state)</th>
<th>Lower limit</th>
<th>Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerular filtration rate (L/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary sodium excretion rate (mEq/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extracellular fluid volume (L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24h urine flow (L/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma sodium concentration (mEq/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal blood flow (L/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal vascular resistance (mmHg*min/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filtration fraction (ratio)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean circulatory filling pressure (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total peripheral resistance (mmHg*min/L)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Additional Virtual Patients generated from pure phenotype to represent the range of patient characteristics in clinical study.

Virtual Population characterizes range of kidney damage due to disease.

- Baseline glycemia
- Baseline BP
- Baseline GFR
- Baseline UACR
Generated VPs have a distribution of physiological characteristics over the mechanistic search axes

- Five mechanistic axes were utilized to generate initial VP diversity
- ~10,000 VPs were created as a result of combining all axes
- ~1000 VPs satisfied the feasible response type (measurement ranges)
- Most variables were normally distributed
Integrated RAAS PhysioLab validated against AVOID

AVOID: study design

Randomization

- Aliskiren 150 mg
- Placebo
- Losartan 100 mg antihypertensive therapy

Open-label

12–14 weeks

Double-blind

0

Week: 12

Week 24

Double-blind, randomized, placebo-controlled study in hypertensive patients with type 2 diabetes and nephropathy
AVOID: Aliskiren in the Evaluation of Proteinuria in Diabetes

- Designed to investigate whether dual intervention with aliskiren added to current optimal ARB treatment would provide additional renal protection compared with the addition of placebo by evaluating change in urinary albumin/creatinine ratio (UACR).

- **Primary endpoint:** change in UACR from baseline to week 24 endpoint with aliskiren added to losartan 100 mg once daily and optimal antihypertensive therapy, compared with addition of placebo.
**STEP1: AVOID Virtual Patient cohort chosen to match baseline characteristics of the study population**

<table>
<thead>
<tr>
<th></th>
<th>Clinical</th>
<th>Simulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>599</td>
<td>167</td>
</tr>
<tr>
<td><strong>MAP (mmHg)</strong></td>
<td>97 ± 9.3</td>
<td>98 ± 8.5</td>
</tr>
<tr>
<td><strong>eGFR (ml/min)</strong></td>
<td>68.5 ± 25.7</td>
<td>68.5 ± 14.5</td>
</tr>
<tr>
<td></td>
<td>&gt; 30</td>
<td>&gt; 30</td>
</tr>
<tr>
<td><strong>Albuminuria (mg/g)</strong></td>
<td>713 (634-802)</td>
<td>718 ± 115</td>
</tr>
<tr>
<td></td>
<td>&gt; 300</td>
<td>&gt; 300</td>
</tr>
</tbody>
</table>

Clinical data from Parving et al, NEJM, 2008 (AVOID)
STEP 2: Reproduce study protocol (therapy, duration) in model

Predicted time course of UACR decline match with AVOID results

Clinical Outcome

AVOID Simulation

Parving et al., NEJM, 2008, 2433-46

UACR: Urinary albumin/creatinine ratio
RAAS Hypertension Platform is still work-in-progress

The current RAAS Hypertension Platform supports generation of many virtual patients exhibiting:
- Disease progression patterns that take into account pathophysiological diversity of hypertensive and diabetic subjects
- Diverse baseline characteristics that correspond to inclusion criteria of patients recruited in clinical trials

Integrated RAAS Hypertension Platform enables a wide range of simulations and hypothesis testing
- RAAS and non-RAAS based therapies
- Single and combination therapies

This approach could complement pharmaco-statistical models

Several computational and methodological challenges
A Systems Approach to Accelerating the Pharmaceutical Industry Pipeline: Competitive Preclinical and Clinical Modeling of SGLT2i Drug Development

Ghosh, Avijit¹; Nucci, Gianluca¹; Haddish-Berhane, Nahor¹; Maurer, Tristan¹; Chen, Yu¹; DaSilva-Jardine, Paul¹; Lo, Arthur²; Reed, Mike²

¹Pfizer, United States;
²Entelos, United States
The Sodium-Glucose Cotransporter 2 (SGLT2), a novel therapeutic target for improving glucose control in type 2 diabetes mellitus (T2DM), plays a major role in the reabsorption of glucose by the kidney.

Pfizer has developed an SGLT2 specific systems model within the Entelos PhysioLab Platform establishing a link between the biomarker Urinary Glucose Excretion (UGE) in healthy volunteers (HV) and improvements in glycemic control and body weight (BW) in longer term studies in T2DM with the aim of improving decision-making for the Pfizer internal compound with regards to clinical trial design.

Using publically disclosed PK/PD profile data on HV and T2DM patients, we have developed a mechanism-based systems model of SGLT2 inhibition that accounts for the simultaneous lowering of the renal glucose excretion threshold and maximum transporter capacity.
The model has been calibrated using single/multiple dose trials and validated by comparing predictions of efficacy against published 12 week trials.

Specifically: a T2D Virtual Patient cohort with variability in A1C, glomerular filtration (GFR) and renal glucose threshold has been used to ensure consistency with the reported baseline variability in the clinical studies.

Phase I and Phase II clinical trial protocols have been simulated in the PhysioLab (single/multiple ascending dose trials in healthy and T2D subjects, 12-week chronic dosing in T2D patients) and the results have been compared to reported data for UGE, A1C and BW to assess model calibration.
The developed SGLT2 specific systems model reproduces various publically disclosed data sets in different populations and study durations, providing a quantitative relationship between the mechanism biomarker (UGE) and the long-term endpoint (A1c).

Further, as we have been successful in representing the Pfizer compound PK/PD in the FIH trial using UGE excretion time course data, we are able to tune drug potency and maximal effects in real time.

The developed model provides the quantitative link established by the competitor SGLT2i clinical data to project efficacy in T2D patients from the observed Pfizer FIH UGE data and effectively project Phase II doses out of a single dose escalation study.

Further it has enabled the optimization of doses and dosing regimen for clinical trial design of the Pfizer SGLT2i taking full advantage of studies conducted in house, allowing us to develop strategies that optimize the efficacy and tolerability of our clinical candidate.
Mechanism of Action

SGLT2 inhibitors promote Urinary Glucose Excretion Leading to:

- Plasma Glucose (PG) Lowering
- Weight Loss
- Favorable Blood Pressure Lowering

Urinary Glucose Excretion (UGE) provides a readily accessible mechanism-based biomarker for clinical assessment

\[
\frac{\partial C(x,t)}{\partial t} = -v \frac{\partial C(x,t)}{\partial x} - \frac{V_{\text{max}}C(x,t)}{C(x,t) + K_m(1 + I/K_i)}
\]

\[\text{reaction/flow} \quad \text{reabsorption}\]
Entelos Overview
SGLT2i

Systems Modeling used to predict human response and improve decision making throughout pipeline.
Entelos Overview
SGLT2i

Systems Modeling used to predict human response and improve decision making throughout pipeline.
Pharmacokinetic Implementation

Methods

- Clinical PK data from:
  - FIH:B1521001 (Fasted)
  - MD:B1521002 (Fed)
- A two-compartment, first-order absorption, first-order elimination PK model was created using population PK parameters fitted from these data.

PK was assumed as the population mean (derived from published popPK).

Summary

- Fasted PK model parameter values: (Nondisclosed)
- Fed PK model parameter values: (Nondisclosed)

DAPA PK:

- PK model parameter values taken from literature.
Qualitative relationship between plasma glucose and urinary glucose excretion

- Urinary glucose appearance is a function of:
  - GFR: Glomerular Filtration Rate
    \[60 - 135 \text{ ml/min}\]
  - RGT: glucose reabsorption threshold
    Baseline Threshold 200 - 275
    Baseline Saturation 375 - 450
    Baseline Maximum 295 - 360
  - Plasma glucose

- In T2D virtual patients, the impact of variability in GFR and RGT on SGLT2 inhibitor efficacy was explored.

An increase in RGT (i.e., increased SGLT2 expression) was generally required to eliminate UGE in untreated T2D virtual patients.

\[\frac{dUGE}{dt} = GFR \cdot K_m' \cdot \text{LambertW} \left( \frac{PG(t) \cdot e^{\frac{v_{\text{max}}}{K_m'}}}{K_m'} \right)\]
Predicted A1c/ BW changes (DAPA)