SimulationsPlus

What's New at Simulations Plus, Your Partner in Winning, for Exposure and Safety Assessment!

SOT Lunch

and ~~Learn~~ Fun!

March 11, 2024

Session Topics

- *Simulations Plus Overview and News*
- *Machine Learning / AI + PBPK + QST: What's the Fuss?*
- *Exposure and Property Prediction Updates*
- *Bridging Exposure to Safety Outcomes for Therapeutic Development*
- *Questions Please!*

Who We Are

NASDAQ: SLP

- **Cheminformatics**
  Software & Services
- **PBPK**
  Software & Services
- **Quantitative Systems Pharmacology (QSP)**
  Software & Services
- **Clinical Pharmacology & Pharmacometrics**
  Software & Services
- **Regulatory Strategies**
  Services

200+
Employees Worldwide

>25 yrs.
Established In 1996

>280 Pharmaceutical, biotechnology, chemicals, cosmetics, and consumer goods companies in the U.S., Europe, Asia, and South America

Complementary Solutions

Decrease development uncertainty, cost, time, and failure rates.

Clinical Pharmacology & Pharmacometrics

NCA

Exposure Response

Dose Optimization

Regulatory/ Post Market

Approval

PBPK / PBBM

QSP: Inflammatory, Immune-Oncology, & Autoimmune Diseases

QST: Safety

DDIs

Population Predictions

PopPK

PK/PD

Food Effects

Product Design

Safety

Pediatric Predictions

AIDD

PhysChem

HTPK

Local & Systemic Exposure

IVIVC & Virtual BE

Efficacy

AP

ADME

Toxicity

G+

First-In-Human

AI / ML Cheminformatics

Model Integrated Data

Empirical Data

"...combining models and data results in higher confidence in clinical performance at an earlier time in development."

U.S. Food & Drug Administration

Confidence Level on Clinical Performance

Time

S+

What's it Like to Work with Us?

We believe the relationships we build with our clients are critical for mutual success

A highly interactive collaboration not only allows us to deliver results as quickly as possible, but also ensures a higher quality deliverable

- Regular interactions ensure the relevancy of results as the knowledge-base continues to evolve
- Transparency provided by progress updates eliminates surprises
- Synergies come from a shared knowledge-base of expertise and experience
- Involvement, participation, and input from stakeholders outside of M&S is welcome

THALES

Hot Off the Presses…..

March 28, 2023 8:30 AM

Simulations Plus Enters New Strategic Collaboration to Discover Anticancer Therapies Through Its

July 13, 2023 8:30 AM

Simulations Plus Releases ADMET Predictor® 11

January 30, 2024 8:30 AM

Simulations Plus Releases GastroPlus® Version 9.9

June 20, 2023 8:00 AM

Simulations Plus Acquires Immunetrics to Expand its Immunology and Oncology Drug Dev

February 13, 2024 9:15 AM

Simulations Plus Launches Corporate Development Initiative

February 15, 2024 8:30 AM

Simulations Plus Extends Collaboration with Major Toxicology Research Agency

Research project with NIEHS includes focus on qualification of in silico methods for prioritization, assessment of risk, and identification of safety margins for chemical use

Simulations Plus, Inc . (Nasdaq: SLP) ("Simulations Plus"), a leading provider of modeling and simulation solutions for the pharmaceutical, biotechnology, chemicals, and consumer goods industries, today announced an extension to the formal agreement with the Translational Toxicology Division at the National Institute of Environmental Health Sciences (NIEHS) to support the rapid safety assessment of chemicals in animals and humans.

How to Engage with SLP, Here and Elsewhere?

andrew.mueller@simulations-plus.com – Director, Business Development

- **Simulations Plus Website:**

https://www.simulations-plus.com/

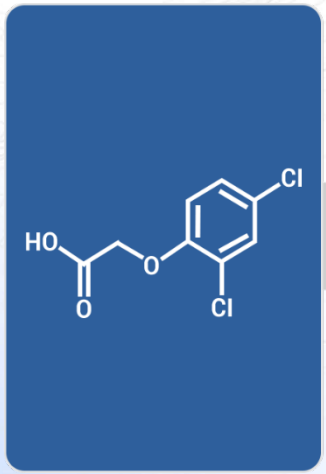
- **Resource Center (publications, webinars, posters, etc…)**

https://www.simulations-plus.com/resource-center/

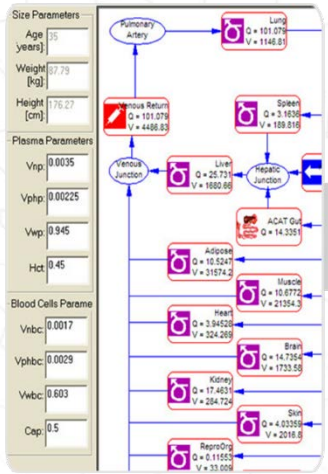
- **Events! (workshops, webinars, conferences, training, etc…)**

https://www.simulations-plus.com/events/

The Machine Learning / PBPK / QSP(T) Marriage… A Winning Combination!



Permeability, solubility vs. pH, pKa(s), logD vs. pH, Fup, blood:plasma ratio, tissue Kps, CLint, CLfilt



Local & systemic exposure, drug distribution, parent and metabolite levels, patient variability

Quantitative Structure Activity Relationships (QSAR)

ADMET Predictor™

Physiologically-Based Pharmacokinetics (PBPK)

GastroPlus™

Quantitative Systems Pharmacology/Toxicology (QSP/QST)

DILIsym®

RENAsym™

CONGRESS.GOV | Advanced Searches | Browse

Search Tools | Support | Sign In

Legislation | Congressional Record | Committees | Members

Legislation | Examples: hr5, sres9, "health care" | MORE OPTIONS

Home > Legislation > 117th Congress > S.5002

Citation | Subscribe | Share/Save | Site Feedback

S.5002 - FDA Modernization Act 2.0

117th Congress (2021-2022)

BILL | Hide Overview ✖

Sponsor: Sen. Paul, Rand [R-KY] (Introduced 09/29/2022)

Latest Action: House - 09/29/2022 Held at the desk. (All Actions)

Tracker: Introduced | Passed Senate

More on This Bill

CBO Cost Estimates [0]

Subject — Policy Area:

Health

View subjects »

Physiological
Pharmacol
Analyses — F
Conte
Guidance for

FDA Guidance D

2018

ance document on the
erisation, validation and
of Physiologically Based
BK) models for regulatory
purposes

OECD

idance Document

2021

Summary (2) | Text (2) | Actions (4) | Titles (3) | Amendments (0) | Cosponsors (11) | Committees (0) | Related Bills (2)

Summary: S.5002 — 117th Congress (2021-2022)

All Information (Except Text)

Listen

There are 2 summaries for S.5002. Passed Senate (09/29/2022) Bill summaries are authored by CRS.

Shown Here:
Passed Senate (09/29/2022)

FDA Modernization Act 2.0

This bill authorizes the use of certain alternatives to animal testing, including cell-based assays and computer models, to obtain an exemption from the Food and Drug Administration to investigate the safety and effectiveness of a drug.

The bill also removes a requirement to use animal studies as part of the process to obtain a license for a biological product that is biosimilar or interchangeable with another biological product.

SimulationsPlus

What Else Is Driving Increased Adoption of M&S? Experimental and Study Costs!

Prompts written into ChatGPT 4: 02Mar2024

Costs continue to rise at high rates.

Stop thinking of M&S as an expense… start thinking of it as an investment!

Basic Toxicity Tests

•**Acute Toxicity Studies:** Costs can range from $5,000

route c

the spe

•**Skin a**

tests ca

More Complex Toxicity Tests

•**Subchronic (90-day) Toxicity Studies:** These

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Reprod

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•**Reproductive Toxicity Studies:** These studies can cost between $300,000 and $1 million, depending on the complexity and species used.

•**Endocrine Disruptor Screening:** These tests can vary widely in cost, from $20,000 for simple assays to over $1 million for a full set of studies.

GastroPlus®/ADMET Predictor®: By the Numbers…

200+
Companies licensing worldwide

15+
Regulatory agencies with reviewers trained on software

350+
Universities in 50+ countries with access to software

120+
Services projects executed over past 12 months

700+
Scientists received software training over past 12 months

90+
Peer-reviewed journal publications over past 12 months

Our ML/PBPK Solutions Are Validated Throughout Your Product's Lifecycle

(1000+ peer-reviewed journal articles reference different applications)

Archives of Toxicology (2023) 97:2659–2673
https://doi.org/10.1007/s00204-023-03576-3

TOXICOKINETICS AND METABOLISM

Physiologically based pharmacokinetic model combined with reverse dose method to study the nephrotoxic tolerance dose of tacrolimus

Limin Cai[1,2] · Meng Ke[1,2] · Han Wang[1,2] · Wanhong Wu[1,2] · Rongfang Lin[1,2] · Pinfang Huang[1,2] · Cuihong Lin[1,2]

Received: 23 May 2023 / Accepted: 2 August 2023 / Published online: 12 August 2023

Abstract
Nephrotoxicity is the most common side effect that severely limits the clinical application of tacrolimus (TAC), an immunosuppressive agent used in kidney transplant patients. This study aimed to explore the tolerated dose of nephrotoxicity of TAC in individuals with different *CYP3A5* genotypes and liver conditions. We established a human whole-body physiological pharmacokinetic (WB-PBPK) model and validated it using data from previous clinical studies. Following the injection of 1 mg/kg TAC into the tail veins of male rats, we developed a rat PBPK model utilizing the drug concentration–time curve obtained by LC–MS/MS. Next, we converted the established rat PBPK model into the human kidney PBPK model. To establish renal concentrations, the $BMCL_5$ of the in vitro CCK-8 toxicity response curve (drug concentration range: 2–80 mol/L) was extrapolated. To further investigate the acceptable levels of nephrotoxicity for several distinct CYP3A5 genotypes and varied hepatic function populations, oral dosing regimens were extrapolated utilizing in vitro-in vivo extrapolation (IVIVE). The PBPK model indicated the tolerated doses of nephrotoxicity were 0.14–0.185 mg/kg (CYP3A5 expressors) and 0.13–0.155 mg/kg (CYP3A5 non-expressors) in normal healthy subjects and 0.07–0.09 mg/kg (CYP3A5 expressors) and 0.06–0.08 mg/kg (CYP3A5 non-expressors) in patients with mild hepatic insufficiency. Further, patients with moderate hepatic insufficiency tolerated doses of 0.045–0.06 mg/kg (CYP3A5 expressors) and 0.04–0.05 mg/kg (CYP3A5 non-expressors), while in patients with moderate hepatic insufficiency, doses of 0.028–0.04 mg/kg (CYP3A5 expressors) and 0.022–0.03 mg/kg (CYP3A5 non-expressors) were tolerated. Overall, our study highlights the combined usage of the PBPK model and the IVIVE approach as a valuable tool for predicting toxicity tolerated doses of a drug in a specific group.

Keywords Tacrolimus · Physiologically based Pharmacokinetics · IVIVE · Nephrotoxicity

Naga et al. (2022)
4100+ downloads!

JOURNAL OF TOXICOLOGY AND ENVIRONMENTAL HEALTH, PART A
2023, VOL. 86, NO. 13, 421–433
https://doi.org/10.1080/15287394.2023.2208593

Taylor & Francis
Taylor & Francis Group

Estimated Dermal Penetration of Tetrachlorvinphos (TCVP) in Humans Based on *In Silico* Modeling and *In Vitro* and *In Vivo* Data

William Reifenrath[a], John Ross[b], Wilfred Maas[c], Joseph Conti[d], Jeffrey H. driver[e], and Michael Bartels[f]

[a]Stratacor, Inc, Novato, CA, USA; [b]risksciencs.net, LLC, Sacramento, CA, USA; [c]Charles River Laboratories Den Bosch BV, The Netherlands; [d]Hartz Mountain Corp, Secaucus, NJ, USA; [e]risksciences.net, LLC, Longboat Key, FL, USA; [f]ToxMetrics.com, LLC, Midland, MI, USA

ABSTRACT
Tetrachlorvinphos (TCVP) is the pesticidal active ingredient in some collars for dogs and cats. The objective of this study was to provide a refined estimate of dermal penetration of TCVP in humans using *in silico* predictions as well as *in vitro* and *in vivo* data. The *in vivo* dermal absorption of TCVP was previously studied in the rat and shown to be saturable, ranging from 21.7% (10 μg/cm^2) down to 3% (1000 μg/cm^2) Subsequent *in silico* predictions were conducted for rats and humans to provide initial evaluations of species and dose-dependent differences in dermal absorption. A definitive comparison of TCVP systemic exposure in rat and human following dermal application was then conducted via a standard *in vitro* assay. TCVP dose levels of 10, 100, or 1000 μg/cm^2 were applied to excised rat and human skin mounted in flow-through diffusion cells. The vehicle was 1% hydroxypropylmethylcellulose (HPMC) in water. An additional 5 μg/cm^2 dose was applied to excised human skin only. The *in vitro* dermal absorption of TCVP was also assessed from artificial sebum at dose levels of 5, 10, or 100 μg/cm^2 applied to human skin only. Utilizing the so-called triple pack approach with *in vitro* and *in vivo* rat data and *in vitro* human data, dermal absorption for TCVP was calculated for humans. *In silico* modeling indicated absorption of TCVP through human skin might be 3- to 4- fold lower than rat skin at all application levels, with a maximum dermal absorption of 9.6% at the lowest exposure of 10 μg/cm^2, down to 0.1% at 1000 μg/cm^2. Similar species differences were also found in the definitive *in vitro* absorption assays. Modeling overestimated TCVP human dermal absorption (9.6%) as compared to excised human skin results (1.7%) for the HPMC vehicle at the lowest exposure (10 μg/cm^2), with better agreement at the higher exposures. Conversely, modeling accurately predicted rat dermal absorption (27.9%) as compared to *in vivo* rat results (21.7%) at the lowest exposure in HPMC, with diminished agreement at the higher exposures. As a first approximation, *in silico* estimates of dermal absorption are useful; however, these tend to be more variable than *in vitro* or *in vivo* measurements. TCVP dermal penetration measured *in vitro* was lower in 1% HPMC vehicle as compared to artificial sebum. For the 1% HPMC vehicle, *in vitro* rat dermal absorption was similar to data obtained for *in vivo* rats, giving confidence in the triple pack approach. In consideration of the triple pack approach, estimated human dermal absorption from 1% HPMC was ≤2%. Based upon excised human skin determinations directly, estimated human dermal absorption of TCVP from artificial sebum was ≤7%.

Keywords
Tetrachlorvinphos; *in vitro* rat; human and *in silico* dermal absorption

Miller et al. (2019)
90+ citations!

Tistaert et al. (2018)
50+ citations!

Archives of Toxicology (2023) 97:1547–1575
https://doi.org/10.1007/s00204-023-03480-w

REGULATORY TOXICOLOGY

Next generation risk assessment of human exposure to estrogens using safe comparator compound values based on in vitro bioactivity assays

Tessa C. A. van Tongeren[1] · Si Wang[1] · Paul L. Carmichael[2] · Ivonne M. C. M. Rietjens[1] · Hequn Li[2]

Received: 23 February 2023 / Accepted: 2 March 2023 / Published online: 22 April 2023

Abstract
In next generation risk assessment (NGRA), the Dietary Comparator Ratio (DCR) can be used to assess the safety of chemical exposures to humans in a 3R compliant approach. The DCR compares the Exposure Activity Ratio (EAR) for exposure to a compound of interest (EAR_{test}) to the EAR for an established safe exposure level to a comparator compound ($EAR_{comparator}$), acting by the same mode of action. It can be concluded that the exposure to a test compound is safe at a corresponding DCR ≤ 1. In this study, genistein (GEN) was selected as a comparator compound by comparison of reported safe internal exposures to GEN to its $BMCL_{05}$, as no effect level, the latter determined in the in vitro estrogenic MCF7/Bos proliferation, T47D ER-CALUX, and U2OS ERα-CALUX assay. The $EAR_{comparator}$ was defined using the $BMCL_{05}$ and EC_{50} values from the 3 in vitro assays and subsequently used to calculate the DCRs for exposures to 14 test compounds, predicting the (absence of) estrogenicity. The predictions were evaluated by comparison to reported in vivo estrogenicity in humans for these exposures. The results obtained support in the DCR approach as an important animal-free new approach methodology (NAM) in NGRA and show how in vitro assays can be used to define DCR values.

Keywords Risk assessment · 3R compliant method · Estrogen receptor · Dietary Comparator · In vitro/insilico approaches

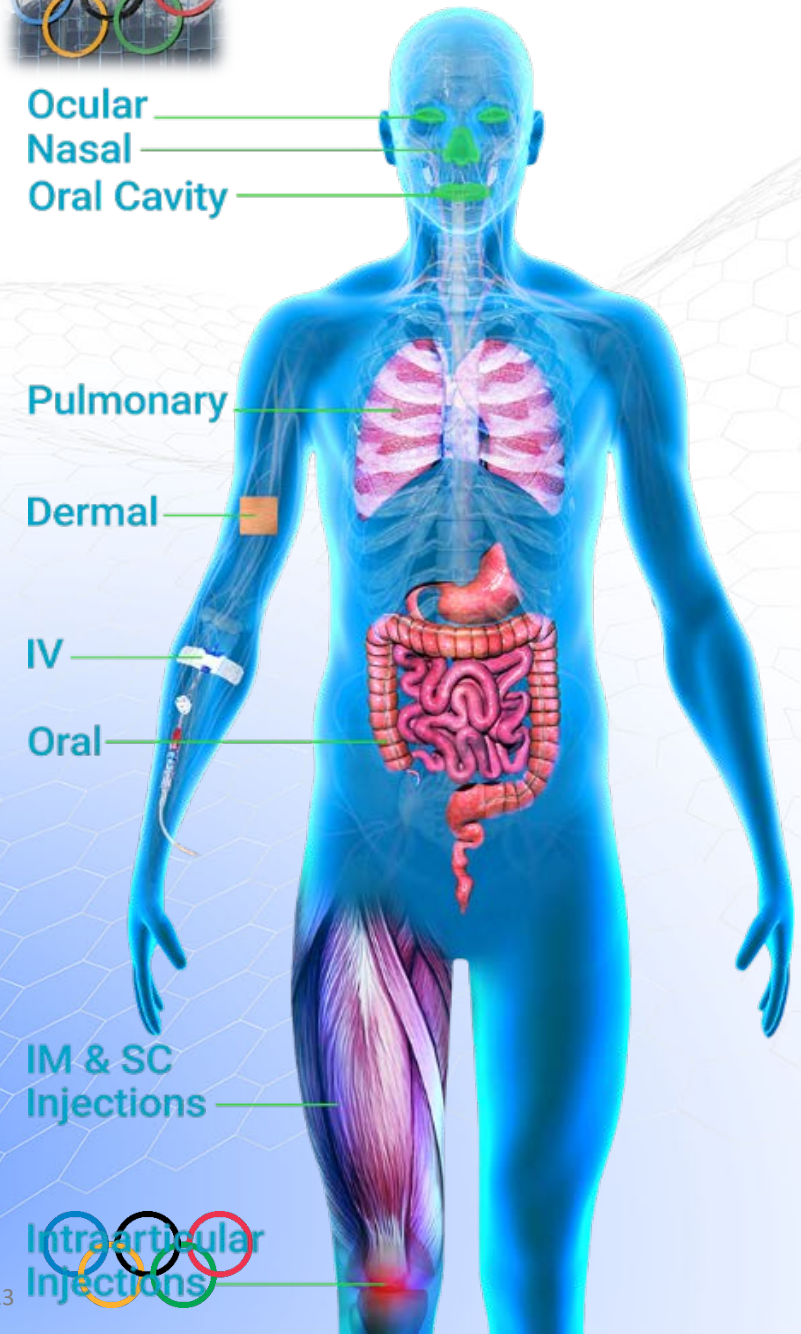
Mitra et al. (2020)
30+ citations!

Ren et al. (2022)
1200+ downloads!

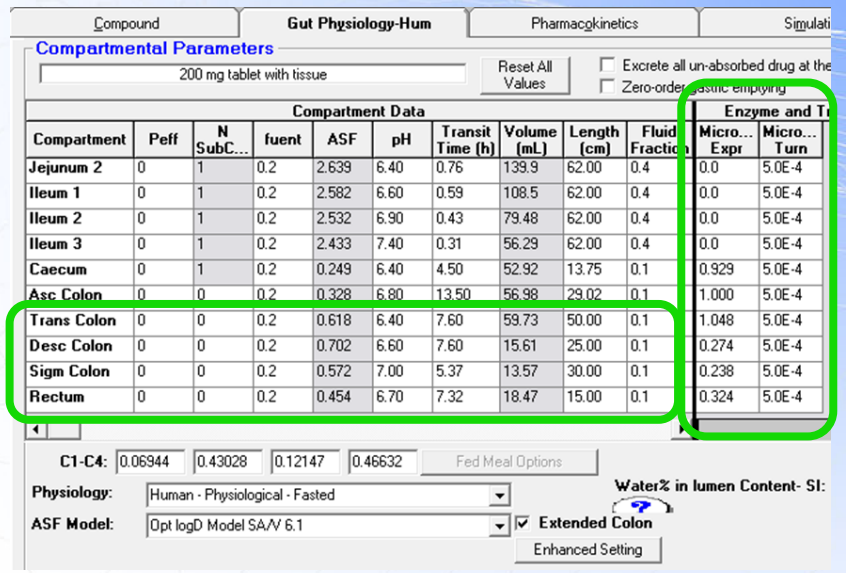
Heimbach et al. (2021)
25+ citations!

Partners Driving PBPK M&S: Active Scientific Collaborations

9 FDA grant awards in 2024!



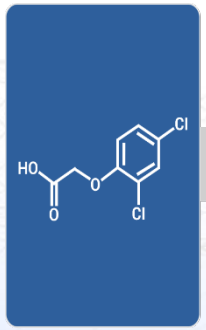
- **FDA: Ocular model extensions**
- **FDA: Oral cavity model extensions**
- **FDA: Pulmonary model extensions**
- **FDA: Dermal model extensions**
- **FDA: Dermal model extensions**
- **ETC (industry): ACAT™ model extensions**
- **FDA: ACAT™ model extensions**
- **FDA: ACAT™ model extensions**
- **FDA: Virtual BE trial workflows**
- **FDA: Long-acting injection model extensions**



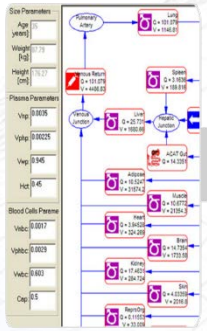
In progress and available for use (example):
Create specific gastrointestinal physiologies to predict local drug behavior in healthy and disease populations

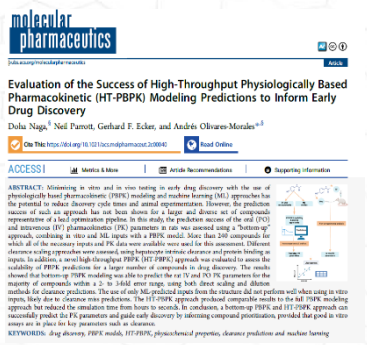
Partners Driving ML Science:
HT-PBPK, AI Drug Design, and Ionization Predictions

HT-PBPK to Support Lead Selection



Permeability, solubility vs. pH, pKa(s), logD vs. pH, Fup, blood:plasma ratio, tissue Kps, CLint, CIfilt Toxicity endpoints





molecular pharmaceutics

Evaluation of the Success of High-Throughput Physiologically Based Pharmacokinetic (HT-PBPK) Modeling Predictions to Inform Early Drug Discovery

Doha Nagy, Neil Parrott, Gerhard F. Ecker, and Andrés Olivares-Morales

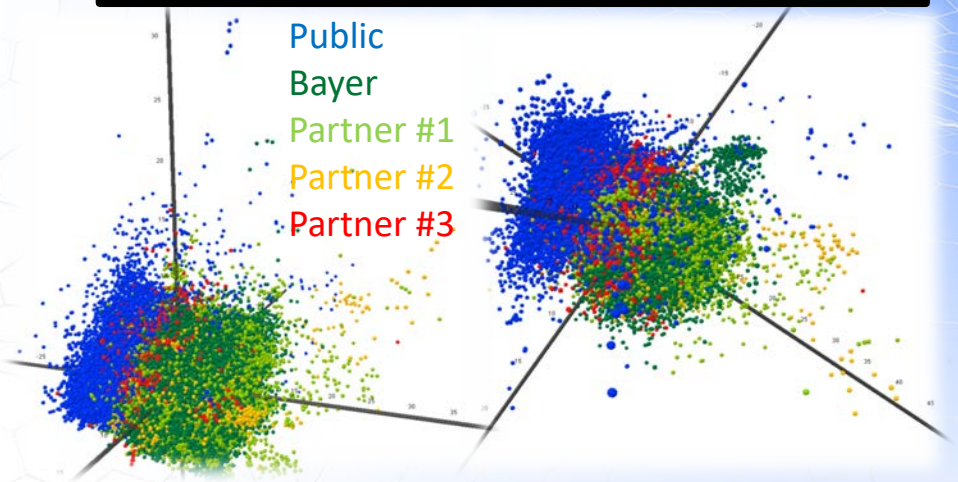
Quantitative Structure Activity Relationships (QSAR)

ADMET Predictor™

Physiologically-Based Pharmacokinetics (PBPK)

GastroPlus™

pKa Collaboration w/Industry Consortium – Including Agrochemical!



AI Drug Design Collaborations

Simulations Plus Enters New Strategic Collaboration to Discover Anticancer Therapies Through Its AI-Driven Drug Design Technology

Drug discovery services partnership with Sino-American Cancer Foundation focuses on the development of actionable hits against the MTHFD2 target

Simulations Plus, Inc. (Nasdaq: SLP), a leading provider of model
today announced that it established a strategic research collabo
leverage Simulations Plus' staff and Artificial Intelligence-driven
support the discovery and design of novel inhibitors of methyler

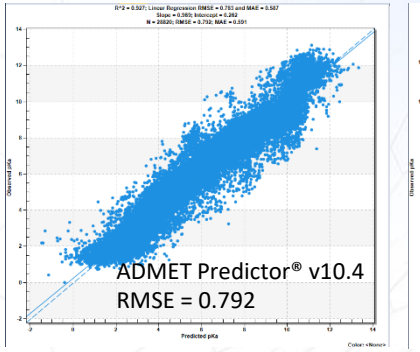
Per the terms of the collaboration, Simulations Plus will develop
MTHFD2, using information from SACF as well as academic and
Early Drug Discovery Services team at Simulations Plus will work
which the lead molecule(s) will be optimized. The new AIDD Mo
compounds that are optimized for potency and other chosen pa
and ensuing rounds of QSAR model building and AIDD optimizat
are achieved.

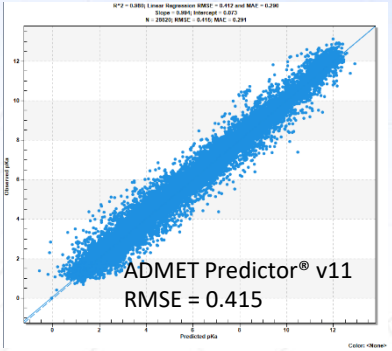
Simulations Plus Enters Partnership to Apply AI/ML Technologies to Design Novel Compounds

Promising intellectual property resulting from the collaboration with Polish Academy of Sciences will be jointly owned for further development opportunities

Simulations Plus, Inc. (Nasdaq: SLP), a leading provider of modeling and simulation software and services for pharmaceutical safety and efficacy, today announced that it entered into a collaborative research agreement with the Institute of Medical Biology of the Polish Academy of Sciences (IMB PAS) to jointly design new compounds for the RORγ/RORγT nuclear receptors using its cutting-edge artificial intelligence (AI) / machine learning (ML) technology in the ADMET Predictor® software platform.

Per the terms of the collaboration, Simulations Plus will deploy the AIDD Module in ADMET Predictor® to create predictive models of inhibition and activation for the human RORγ/RORγT nuclear receptors. The computational and medicinal chemists at Simulations Plus will then interact with researchers at the IMB PAS to define the multi-objective parameters against which the lead molecule(s) will be optimized. The generative chemistry approaches within the AIDD Module will produce novel libraries of virtual compounds with desired combinations of the properties chosen, and the IMB PAS will synthesize and test promising analogs. Emerging intellectual property, in the form of encouraging lead compounds, will be jointly owned by Simulations Plus and IMB PAS for further development opportunities.





SimulationsPlus

2024 Software Roadmap

GastroPlus® v9.9 – January

- ACAT™ model extensions: microbiome-mediated (or general metabolic conversion) in gut lumen
- Improvements to the Biologics Module
- New/improved models in the ADMET Predictor® Module
- Enhancements to the oral cavity/dermal/ocular PBPK models
- … and more!

GastroPlus® X – Spring

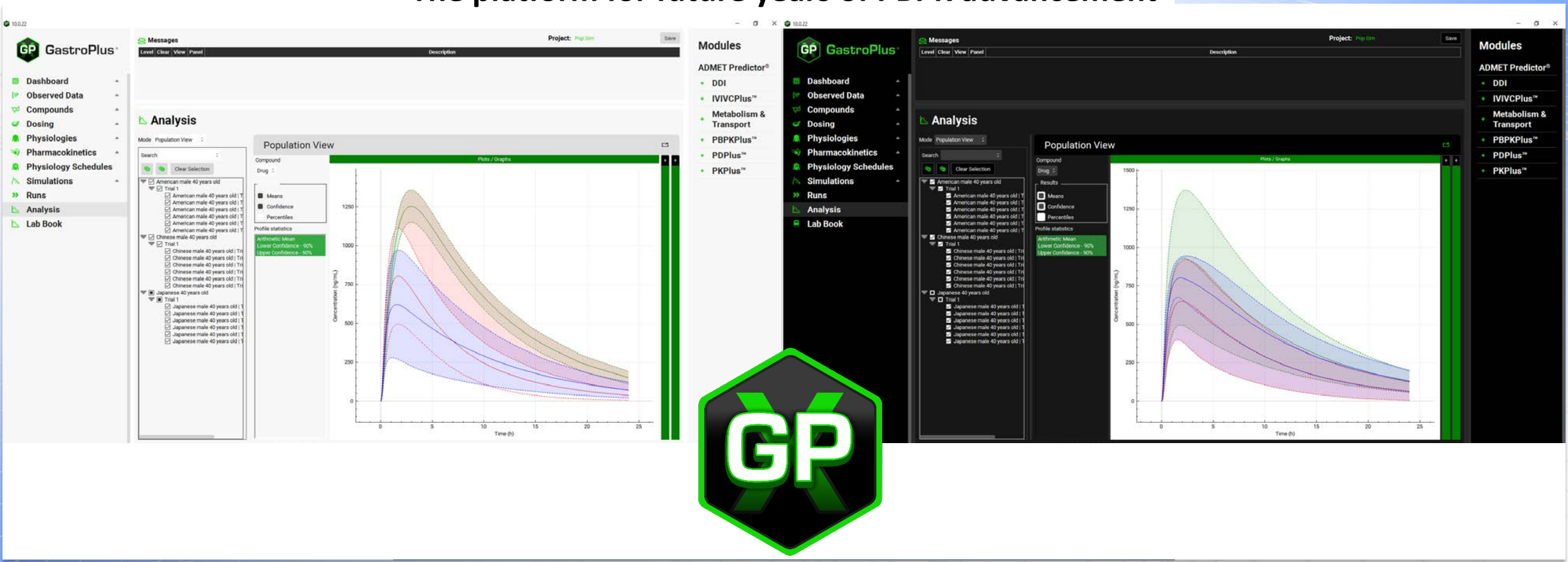
- The next-generation platform – new GUI, workflows, run modes, and more!

ADMET Predictor® v11.5 – Summer

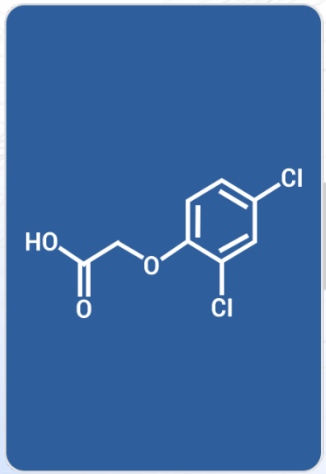
- Rebuilt PCB models – solubility, clearance, and more!
- New models to inform DILIsym simulations
- Enhancements to HTPK Simulation and AIDD modules
- … and more!

GPX = PBPK Advancement Platform

The platform for future years of PBPK advancement



The Machine Learning / PBPK / QSP(T) Marriage… A Winning Combination!



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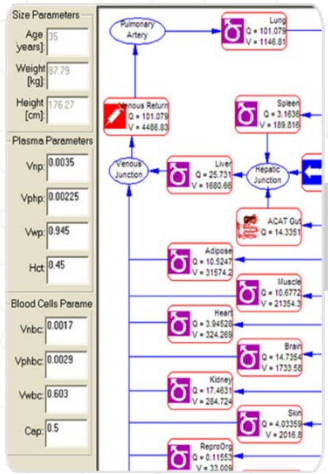

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Quantitative Structure Activity Relationships (QSAR)

ADMET Predictor™

Physiologically-Based Pharmacokinetics (PBPK)

GastroPlus™

Quantitative Systems Pharmacology/Toxicology (QSP/QST)

DILIsym®

RENAsym™

DILIsym & RENAsym QST Software Aids Decisions

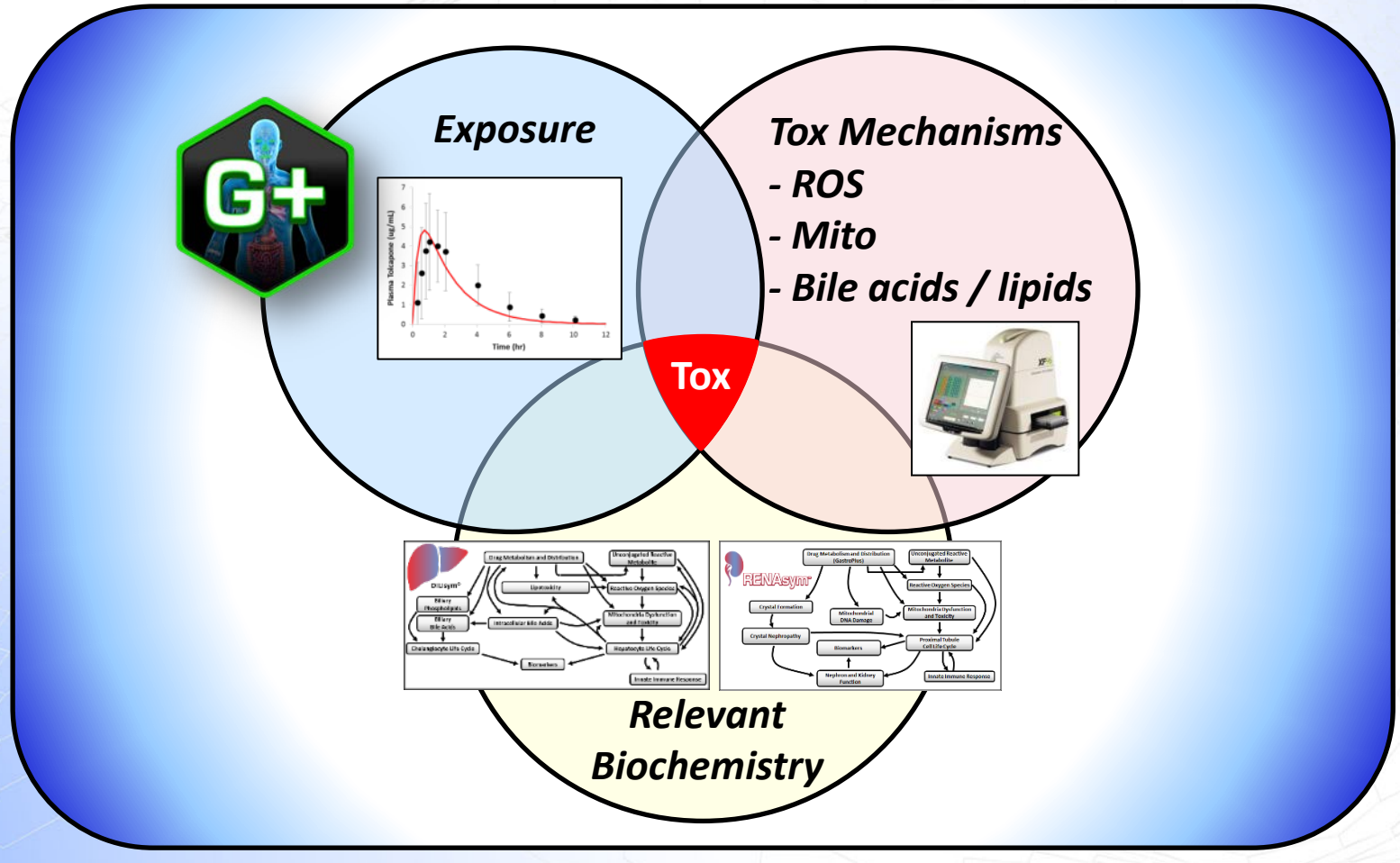
DILIsym® RENAsym™

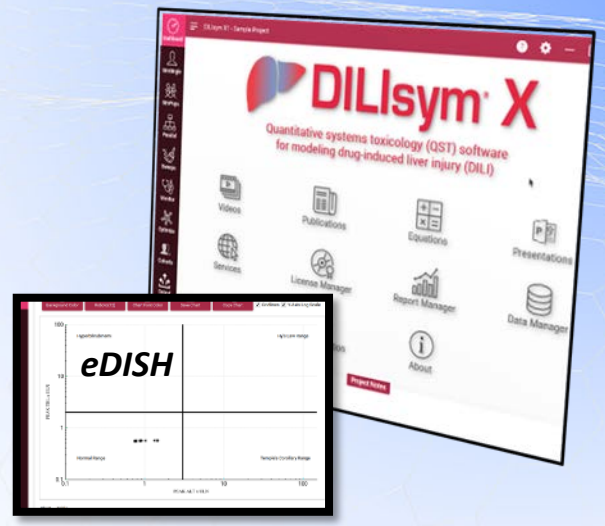
- Predicts drug-induced liver or kidney injury
- Many versions and upgraded released with new science
- Includes mechanistic representation of normal hepatic and renal biochemistry
- Evaluated >80 compounds with 45+ companies overall

So how can DILIsym + RENAsym help my organization?

- Predict DILI / renal liabilities beforehand and save **$$$**
- Choose the lead candidate ***most likely to succeed*** from a DILI and renal safety standpoint
- Communicate with regulators on safety issues with information they have requested from others numerous times and from a platform they license (FDA)
- ***Keep patients safer….***

QST Predicts Tox via the Intersection Between Exposure, Mechanisms, and Inter-Patient Variability





The Proof Is In The Approved Therapies – Liver Safety

UBRELVY (ubrogepant) tablets 50mg 100mg

Nurtec® ODT (rimegepant) orally disintegrating tablets 75 mg

JYNARQUE® (tolvaptan) 15, 30, 45, 60, 90 mg tablets

Epidiolex® (cannabidiol)

De-risked Target

Confidence for Chronic Indication

Turalio® pexidartinib 125 mg capsules

Mechanistic safety insight

Zavzpret™ (zavegepant) nasal spray 10 mg

QULIPTA™ (atogepant) tablets

Veklury® remdesivir 100 MG FOR INJECTION

TYLENOL® Care Without Limits

Addressed regulatory inquiry

Safe dose selection for Ph III

VEOZAH™ (fezolinetant) tablets 45mg

DILIsym Cited in FDA Medical Review of Fezolinetant

MEMORANDUM

Department of Health a
Public Health Service
Food and Drug Adminis
Center for Drug Evaluat

FROM: Jamie Brewer, MI
Clinical Team Lea

THROUGH: Lola Fashoyin-Aje
Deputy Director, D
Steven Lemery, MI
Director, DO3

TO: Christina Chang, MI
Director, Division of
(DUOG)

SUBJECT: NDA 216578- ESN3
treatment of moderate
(VMS) associated wit

CONSULT DATE: June 22, 2022

DATE: January 23, 2023

BACKGROUND

Astella Pharma Global Development, Inc., (Astellas) s
fezolinetant, a small molecule, non-hormonal selective
antagonist that blocks neurokinin B (NKB) binding. NI
that binds preferentially to the neurokinin 3 receptor. E
NKB is elevated in postmenopausal women. NKB/NK3
role in the pathophysiology of hot flushes through inapp
dissipation responses via the thermoregulatory centers in
attenuation of the NKB/NK3R signaling pathway has en
target for the treatment of menopausal hot flushes (poten
estrogen replacement), the safety profile of agents targeti
established. (Jayasena CN, et al. 2015) If approved, fezol
NK3 receptor antagonist in the US.

Astellas submitted three randomized controlled trials (Tria
CL-0302, Trial 2693-CL-0304) to support FDA's assessm
effectiveness of fezolinetant for the proposed indication. T

FORBES > INNOVATION > HEALTHCARE

Menopausal Drug Veozah Features Prominently Among Super Bowl Ads

Joshua Cohen Senior Contributor ⓘ
I write about healthcare policy, with an emphasis on Rx drugs.

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Feb 12, 2024, 12:49pm ES

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Woman having vasomotor symptoms of menopause. GETTY

Drug maker Astellas spent more than $24 million on commercials featuring the menopausal drug Veozah during the 2023 NFL season, culminating in a 60-second spot last night during the Super Bowl.

ewsroom / Press Announcements / FDA Approves Novel Drug to Treat Moderate to Severe Hot Flashes Caused by Menopause

FDA NEWS RELEASE

FDA Approves Novel Drug to Treat Moderate to Severe Hot Flashes Caused by Menopause

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Clinical Review
Theresa H. van der Vlugt, M.D., M.P.H.
Regina Zopf, M.D., M.P.H.
NDA 216578
TRADENAME (fezolinetant) Tablets

patic Safety

n for the liver safety of fezolinetant arose during the conduct of phase 2 clinical
ater incidence of alanine aminotransferase (ALT)/aspartate aminotransferase
were observed in participants receiving fezolinetant active treatment vs.
fezolinetant development for VMS, and other Astellas/Ogeda SA programs,
minotransferase elevations were reported occurring at fezolinetant doses
g daily to a single 900 mg dose. Hepatic enzyme elevations characteristically
en 1-2 months on treatment, and rapidly resolved with discontinuation of
orrelation was observed between exposure to fezolinetant (AUC) and the
erase elevations. Prior to phase 3 development, Astellas conducted
ns Toxicology (QST) modeling (DILIsym) which predicted the adverse hepatic
t phase 2 dosing . Based on these reported findings, phase 3 fezolinetant
mited to 30 and 45 mg fezolinetant dosage strengths.

elopment, Astellas and the Agency agreed upon the following hepatic
tions, participant discontinuation criteria, and enhanced hepatic
oring in phase 3 clinical trials:

Investigating the Potential Hepatotoxicity of ORM-48824 in a Quantitative Systems Toxicology Platform for Liver Safety, DILIsym®

#4359/P144

Pallavi Bhargava[a], Shailendra Tallapaka[a,b], Timo Korjamo[c], Melina Malinen[c], Teija Oinonen[c], Brett A. Howell[a]

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[b] Quantitative Pharmacology & Pharmacometrics, Merck & Co., Inc., Rahway, NJ (current affiliation)
[c] Orion Corporation, Espoo, Finland

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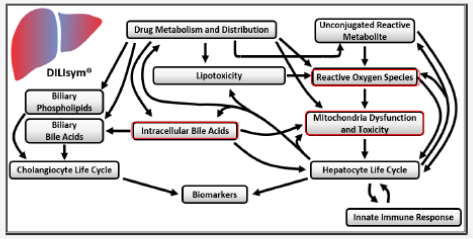
INTRODUCTION

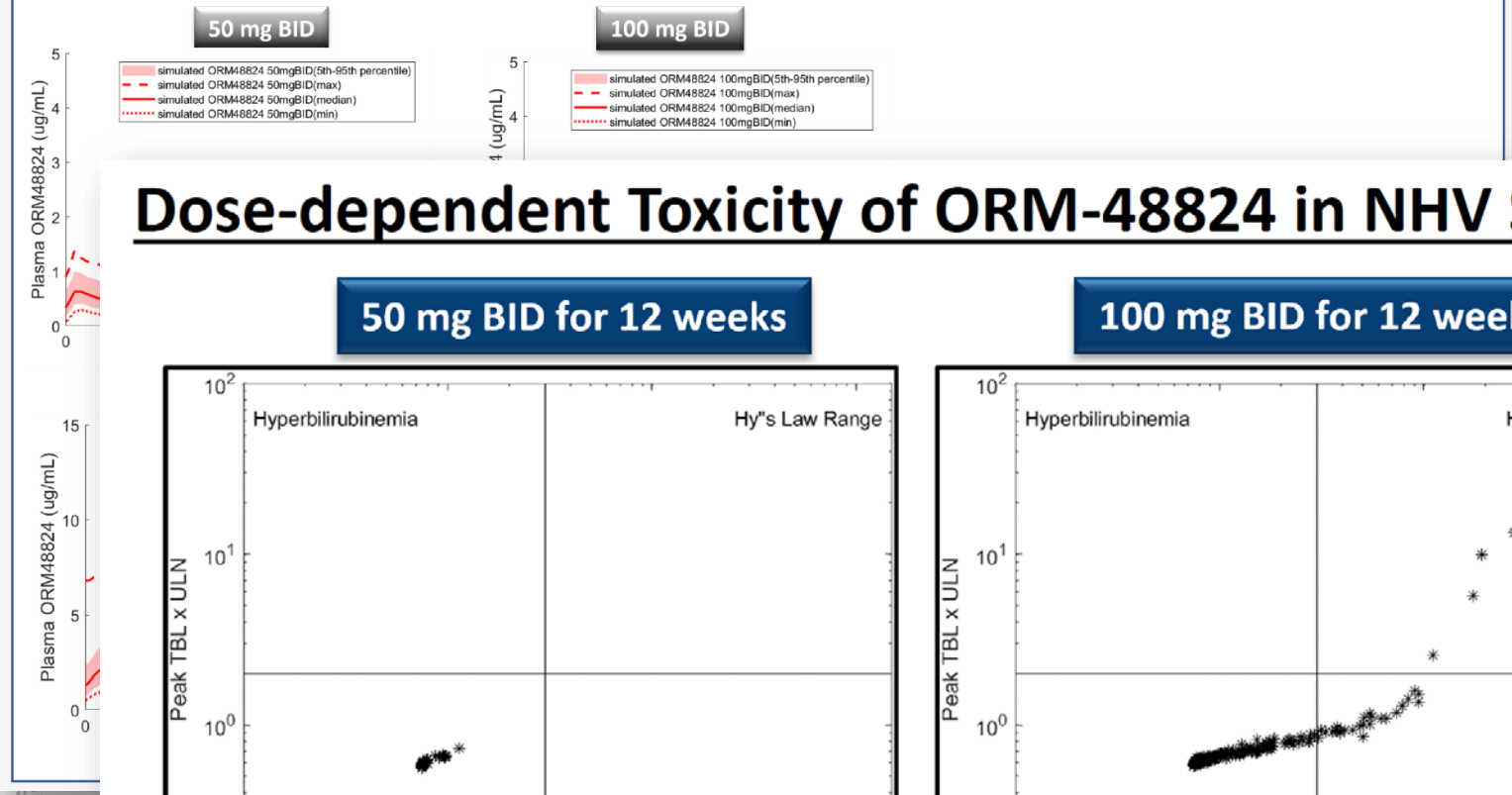
ORM-48824 is a transient receptor potential Ankyrin-1 (TRPA1) antagonist and was initially being developed for patients with diabetic neuropathic pain, osteoarthritis, and other pathophysiological conditions to attenuate pain hypersensitivity. *In vitro* experiments suggested that ORM-48824 may inhibit bile acid transporters and induce mitochondrial dysfunction and oxidative stress, mechanisms that contribute to liver toxicity. DILIsym was utilized to prospectively predict clinical liver toxicity and the dominant toxicity mechanism potentially responsible for any signals predicted.



METHODS

- HepG2 cells were treated with doses of ORM-48824 ranging from 2 to 100 µM and mitochondrial respiration was measured using a Seahorse XFe96 Analyzer
- Reactive oxygen species (ROS) production was measured using high content screening to quantify dihydroethidium staining following ORM-48824 exposure (0.4-200 µM)
- ORM-48824 was administered in human ATP-binding cassette (ABC) efflux (BSEP, MRP3, and MRP4) transporters and in human solute carrier (uptake) transporter NTCP, where the accumulation of a probe substrate was measured.
- A PBPK model was built in GastroPlus 9.8.2® for ORM-48824 and variables with known dependency on species, gender, age, height, weight, or BMI had distributions defined by the built-in Population Estimates for Age-Related Physiology (PEAR Physiology) generator
- MITOsym® was used to parameterize ETC inhibition to *in vitro* mitochondrial respiration studies of ORM-48824 and ROS parameterization was performed in DILIsym
- Doses of 500 mg BID, 250 mg BID, 100 mg BID, and 50 mg BID were simulated for 12 weeks in the NHV SimPops (N=285)
- Mechanistic analysis was conducted by simulating 250 mg BID in a SimCohorts of 32 individuals

Simulated Exposure of ORM-48824



Dose-dependent Toxicity of ORM-48824 in NHV SimPops

CONCLUSION

- DILIsym is comprised of submodels that interact with one another to predict liver injury outcomes. DILIsym for ORM-48824, as well as inner workings of liver physiology to predict the potential for ORM-48824 to ind
- In vitro studies showed that ORM-48824 induces mitochondrial dysfunction, elevation of ROS, and bile acid
- Simulating 50 mg BID, 100 mg BID, 250 mg BID, and 500 mg BID for 12 weeks in in the NHV SimPops in DILI
- No ALT elevations were predicted with 50 mg BID for 12 weeks
- Mechanistic analysis showed that the number of individuals with ALT elevations decrease significantly when the mitochondrial dysfunction mechanism is turned off, suggesting this is the dominant toxicity pathway
- Due to these results and other data gathered by Orion Corporation, ORM-48824 was discontinued due to potential liver toxicity, aiding in drug discovery and liver safety

Modeling and Simulation of Acetaminophen Pharmacokinetics and Hepatic Biomarkers After Overdoses of Extended-Release and Immediate-Release Formulations with DILIsym, a Quantitative Systems Toxicology (QST) Software Platform

B. A. Howell[1], K. Yang[1], J. J. Beaudoin[1], Z. Kenz[1], V. V. Lakhani[1], J. L. Woodhead[1], J. C. Lai[2], C. K. Gelotte[3], S. Sista[2], E. Atillasoy[2,*]

[1]QSP Solutions, Simulations Plus, Inc., RTP, NC; [2]Kenvue, Montgomery Township, NJ; [3]Independent Consultant, Westbrook, CT

*Contact information: eatillas@kenvue.com

Kenvue

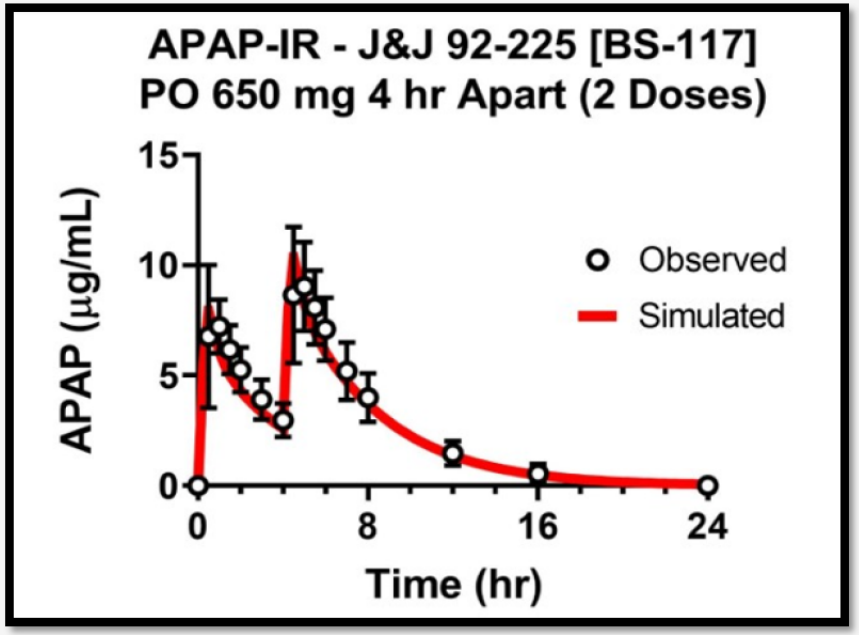
Search

BACKG

- The analg formulatio release pr
- In 2017, suspendin preparatio overdose, pharmaco delayed pl release (IR
- There wa developed formulatio
- In the U (TYLENOL NJ) is desi
- This proje compare various ac (RSTI) scer US APAP-I

METH

- The existin of drug-ind reactive m APAP meta (Fig. 1)
- Exposure-d mediated respectivel
- An APAP-ER model was developed by modifying the representation of APAP absorption in the APAP-IR model to recapitulate the fast- and slow-release from IR and ER layers of the APAP-ER caplet and was verified with clinical data (Fig. 2)
- *In vitro* dissolution of APAP from the IR and ER formulations was experimentally evaluated using different systems (*e.g.*, Tiny-TNO Gastro-Intestinal Model smartificialgut, Tiny-TIMsg)
- These experimental data were used as input for the Z-factor (Takano) dissolution model within GastroPlus® to inform the *in vivo* dose-vs-fraction absorbed (Fa) relationship for APAP-IR and APAP-ER that was subsequently leveraged within the DILIsym model (Fig. 3)
- Simulated populations (SimPops®) representing healthy adults, moderate chronic alcohol users (MCAU), excessive chronic alcohol users (ECAU), and individuals with low glutathione (GSH) were developed and verified using clinical PK and hepatic biomarker data (Fig. 4)
- The DILIsym model was then used to simulate PK and three clinically useful hepatic biomarkers [plasma alanine aminotransferase (ALT), total bilirubin (TB), and international normalized ratio (INR)] after single acute overdoses (3.9, 9.75, 19.5, 32.5, 65, 78 and 100.1 g; Fig. 5; Table 1) and RSTI (3.9, 5.2 and 7.8 g/day; Table 2) of APAP-ER and APAP-IR
- Simulations were carried out in the absence of clinical interventions (*e.g.*, decontamination, N-acetylcysteine treatment), such that they represent worst-case scenarios



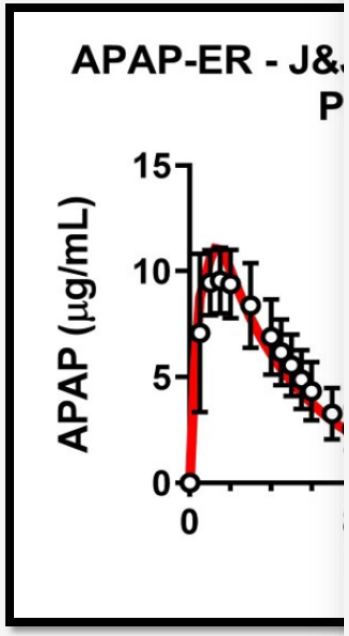


Fig. 4: Calibration and APAP-IR - J&J 92-225 [BS-117]

GastroPlus (solid lines) was reasonably recapitulated by the DILIsym model (dashed lines) of APAP-IR and APAP-ER. USP, United States Pharmacopeia.

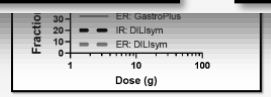


Fig. 5: Simulated mean APAP PK profiles (solid lines) and APAP-IR (dotted lines) i alcohol users, excessive chronic alcohol glutathione. Simulated APAP PK profil Matthew reference line crossing differe IR within each population.

Ingested Dose (g)	AUC$_\infty$ (µg·h/mL) APAP-ER	AUC$_\infty$ (µg·h/mL) APAP-IR	C$_{max}$ (µg/mL) APAP-ER	C$_{max}$ (µg/mL) APAP-IR	Fa APAP-ER	Fa APAP-IR	ALT$_{max}$ (U/L) APAP-ER	ALT$_{max}$ (U/L) APAP-IR	TB$_{max}$ (mg/dL) APAP-ER	TB$_{max}$ (mg/dL) APAP-IR	INR$_{max}$ APAP-ER	INR$_{max}$ APAP-IR
3.9	195.7 (24.10%)	200.0 (23.97%)	32.6 (19.73%)	46.1 (18.67%)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	30.0 (30.00-30.00)	30.0 (30.00-30.00)	0.55 (0.55-0.55)	0.55 (0.55-0.55)	1.0 (1.00-1.00)	1.0 (1.00-1.00)
9.75	542.7 (25.35%)	553.9 (25.44%)	84.5 (19.78%)	103.4 (19.08%)	0.97 (0.95-0.99)	1.00 (0.99-1.00)	36.8 (30.00-201.65)	38.3 (30.00-225.90)	0.55 (0.55-0.59)	0.55 (0.55-0.59)	1.0 (1.00-1.00)	1.0 (1.00-1.00)
19.5	1046.6 (26.78%)	1174.2 (27.02%)	155.7 (20.27%)	201.2 (19.07%)	0.87 (0.81-0.94)	0.97 (0.89-0.99)	272.5 (30.00-4491.62)	421.0 (30.00-6998.37)	0.55 (0.55-2.29)	0.62 (0.55-6.60)	1.0 (1.00-1.86)	1.0 (1.00-4.93)
32.5	1634.6 (27.99%)	1903.2 (28.28%)	234.2 (20.53%)	311.4 (20.27%)	0.77 (0.69-0.87)	0.89 (0.74-0.97)	1268.8 (30.01-8640.56)	1984.7 (32.37-8885.89)	1.12 (0.55-13.86)	1.64 (0.56-12.05)	1.2 (1.00-7.91)	1.5 (1.00-7.92)
65	2841.9 (29.96%)	3255.1 (31.66%)	392.5 (20.83%)	495.6 (22.89%)	0.61 (0.51-0.74)	0.70 (0.50-0.88)	4104.9 (116.74-8894.11)	4756.2 (197.77-8816.65)	3.44 (0.59-15.08)	4.10 (0.59-14.43)	2.5 (1.00-7.90)	2.7 (1.00-7.87)
78	3237.5 (30.59%)	3646.7 (32.59%)	443.7 (21.04%)	545.9 (23.75%)	0.57 (0.46-0.70)	0.64 (0.44-0.84)	4688.0 (176.50-8688.58)	5119.3 (263.87-8741.29)	3.95 (0.59-14.22)	4.53 (0.60-14.88)	2.6 (1.00-7.79)	2.9 (1.00-7.91)
100.1	3822.7 (31.53%)	4190.9 (33.88%)	518.6 (21.54%)	612.9 (24.97%)	0.51 (0.39-0.65)	0.56 (0.36-0.79)	5249.2 (273.63-8800.01)	5398.2 (366.74-8690.06)	4.66 (0.62-14.86)	4.97 (0.61-15.23)	2.9 (1.00-7.92)	3.0 (1.00-7.94)

Table 1 (left) and **Table 2** (right): Comparison of simulated plasma APAP PK parameters and hepatic biomarkers after single overdoses (Table 1) or RSTI (Table 2) of APAP-ER and APAP-IR in healthy adults. On average, APAP exposure after acute overdose or RSTI in healthy adults was predicted to be lower for APAP-ER compared to APAP-IR. Similar ALT, TB and INR levels were predicted for APAP-ER and APAP-IR after overdoses in healthy adults. These findings were similar when making comparisons between APAP-ER and APAP-IR in the compromised adult SimPops (*i.e.*, MCAU, ECAU, low GSH).

Simulated exposure parameters (AUC$_\infty$, C$_{max}$, AUC$_t$ and C$_{max,ss}$) as well as fraction excreted in urine (Fu) for 300 virtual adults in the APAP-ER and APAP-IR SimPops are reported as mean (% coefficient of variation), whereas Fa, and simulated maximum concentrations of hepatic biomarkers (ALT$_{max}$, TB$_{max}$, and INR$_{max}$) are reported as median and range. Baseline biomarker values in the DILIsym model are 30, 0.55 and 1 for ALT (U/L), TB (mg/dL) and INR, respectively.

Parameter	Scenario A (3.9 g/day) APAP-ER	Scenario A (3.9 g/day) APAP-IR	Scenari APAP-ER
AUC$_t$ (µg·h/mL)	55.2 (25.69%)	54.9[a] (25.73%)	56.6 (26.60%)
C$_{max,ss}$ (µg/mL)	11.9 (21.52%)	10.9 (21.45%)	13.7 (22.94%)
AccR	0.97 [0.85-1.18]	1.01 [0.85-1.29]	0.99 [0.85-1.26
Fu APAP (%)	3.2 (23.22%)	3.2 (23.34%)	3.3 (24.20%)
Fu APAP-S (%)	60.3 (13.36%)	60.1 (13.41%)	61.7 (12.58%)
Fu APAP-S (%)	21.7 (28.49%)	22.1 (28.26%)	20.1 (28.73%)
Fu Thiols (%)	9.8 (22.81%)	9.7 (22.88%)	9.8 (22.39%)
Fu Catechols (%)	4.9 (35.64%)	4.9 (35.72%)	5.0 (35.99%)
ALT$_{max}$ (U/L)	31.5 [30.00-137.78]	31.5 [30.00-136.25]	36.0 [30.00-263.33]
TB$_{max}$ (mg/dL)	0.55 [0.55-0.57]	0.55 [0.55-0.57]	0.55 [0.55-0.59]
INR$_{max}$	1.0 [1.00-1.00]	1.0 [1.00-1.00]	1.0 [1.00-1.00]

Ingested Dose (g)	ALT$_{max}$ (U/L) APAP-ER	ALT$_{max}$ (U/L) APAP-IR
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19.5	272.5 (30.00-4491.62)	421.0 (30.00-6998.37)
32.5	1268.8 (30.01-8640.56)	1984.7 (32.37-8885.89)
65	4104.9 (116.74-8894.11)	4756.5 (197.77-8816.65)
78	4688.0 (176.50-8688.58)	5119.3 (263.87-8741.29)
100.1	5249.2 (273.63-8800.01)	5398.2 (366.74-8690.06)

J.C.L., S.S., and E.A. are employees of Kenvue Inc. C.K.G. served as a paid consultant for Kenvue Inc. as part of this work.

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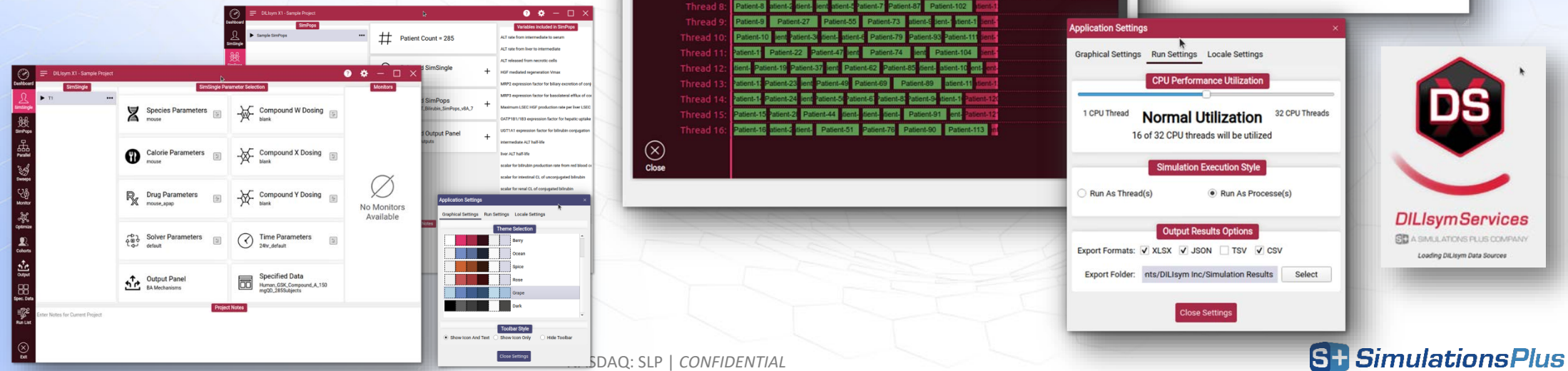
Highlights of DILIsym Version X (DSX)

- Completely new software platform!
  - Much faster and more user friendly
  - Command line and GUI options
  - No reliance on MATLAB runtime or base MATLAB
  - Server/cloud computing capability coming soon…..
- 4 NEW exemplar Compounds included with varying clinical presentations
  - PF-04895162 *(Generaux 2019)*
  - Efavirenz
  - Anastrozole
  - Tamoxifen
- 2 New SimCohorts that include variability in susceptibility to liver injury and biomarker-related parameters (ALT and bilirubin)



How to Engage with SLP, Here and Elsewhere?

andrew.mueller@simulations-plus.com – Director, Business Development

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