DILIsym Services

A SIMULATIONS PLUS COMPANY

Assessing the Potential for Hepatotoxicity for Combination Therapy of Valproate (VPA) and CBD using Quantitative Systems Toxicology (QST)

DILIsym Correctly Predicts CBD ALT Elevations and Evaluates Interaction Mechanism(s)

AASLD FDA DILI Meeting 2021

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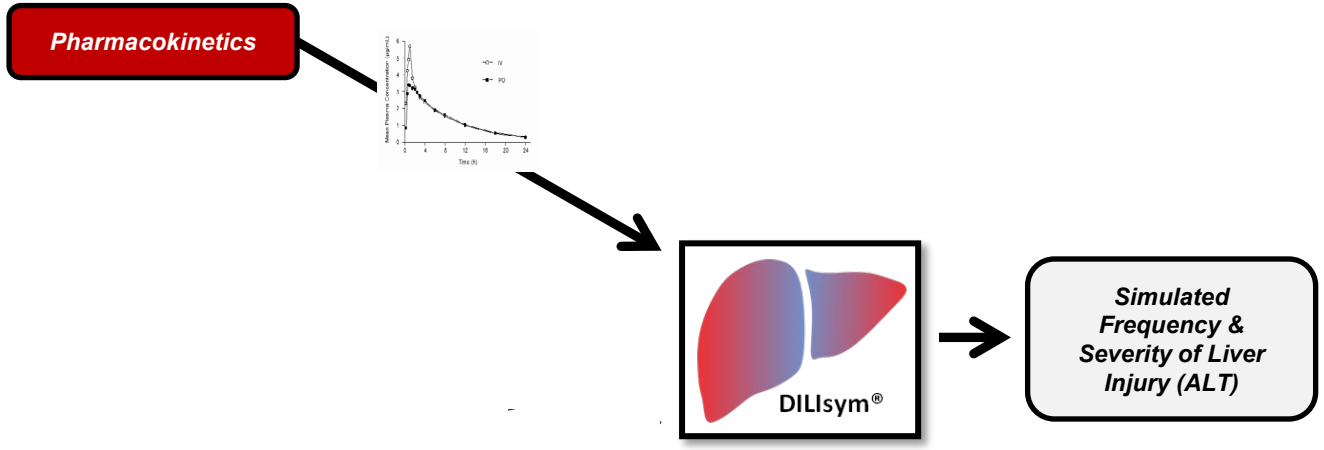
Disclaimer: DILIsym Services are developed and provided as an educational tool based on assessment of the current scientific and clinical information, and accepted approaches for drug safety and efficacy. The resultant data, suggestions, and conclusions ("Guidelines") should not be considered inclusive of all proper approaches or methods, and they cannot guarantee any specific outcome, nor establish a standard of care. These Guidelines are not intended to dictate the treatment of any particular patient. Patient care and treatment decisions should always be based on the independent medical judgment of health care providers, given each patient's individual clinical circumstances.

Project Scenario and Goal

- Epidiolex (highly purified CBD) is efficacious in treating seizures associated with Dravet syndrome (DS), Lennox-Gastaut syndrome (LGS), and Tuberous Sclerosis Complex (TSC)
- In the clinical trials of these patients, ALT elevations were seen in 21% of trial participants taking CBD with concomitant valproate (VPA) compared with 3% in participants not taking VPA [Epidiolex prescription info]
- **<u>GOAL</u>: To identify the mechanism(s) accounting for the higher incidence of ALT elevation observed during concomitant treatment with VPA and CBD by using a Quantitative Systems Toxicology (QST) model of hepatotoxicity (DILIsym®)**
- **<u>HYPOTHESIS</u>: Increased incidence of ALT elevations was due to VPA and CBD (or metabolites of each) inhibiting mitochondrial respiration**

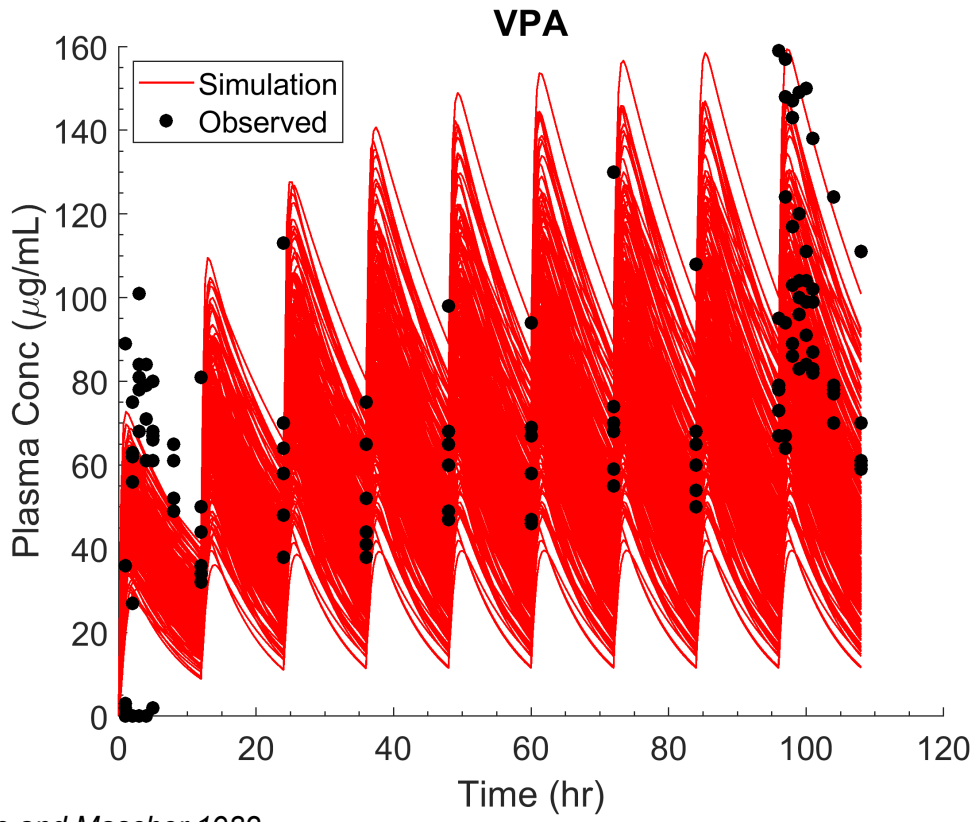
DILIsym Input Data

Exposure



GastroPlus PBPK Models for VPA and CBD Optimized and Validated Against Clinically Measured Plasma Exposure

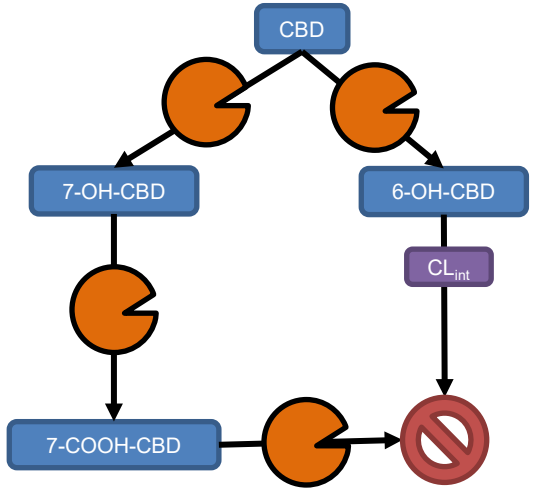
VPA PBPK Model

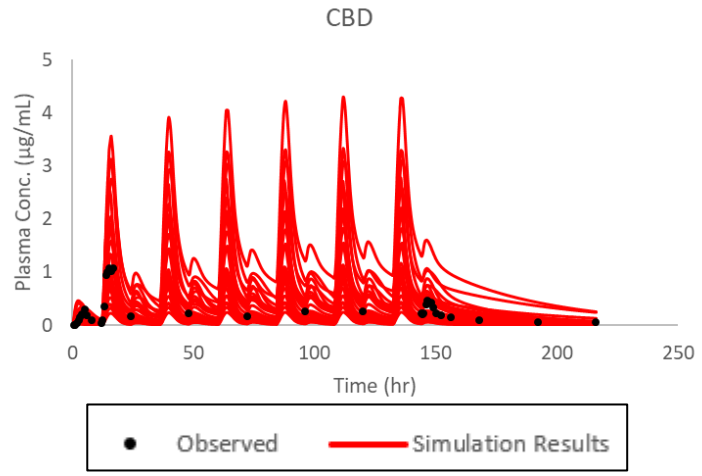


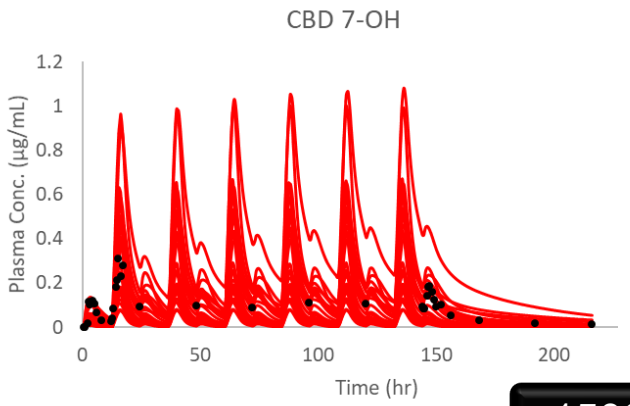
Nitsche and Mascher 1982

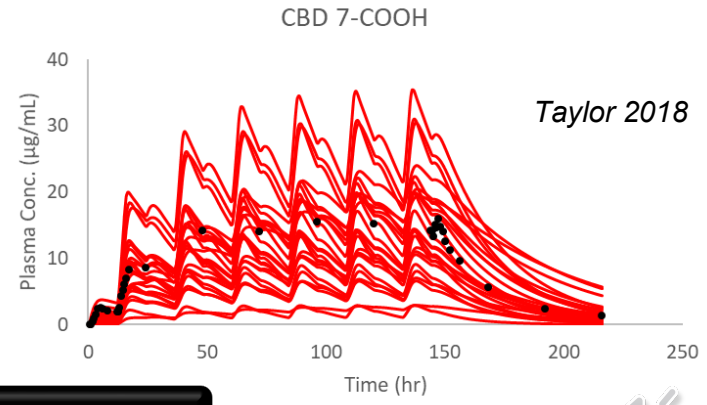
1000 mg BID

CBD Metabolism & PBPK Model









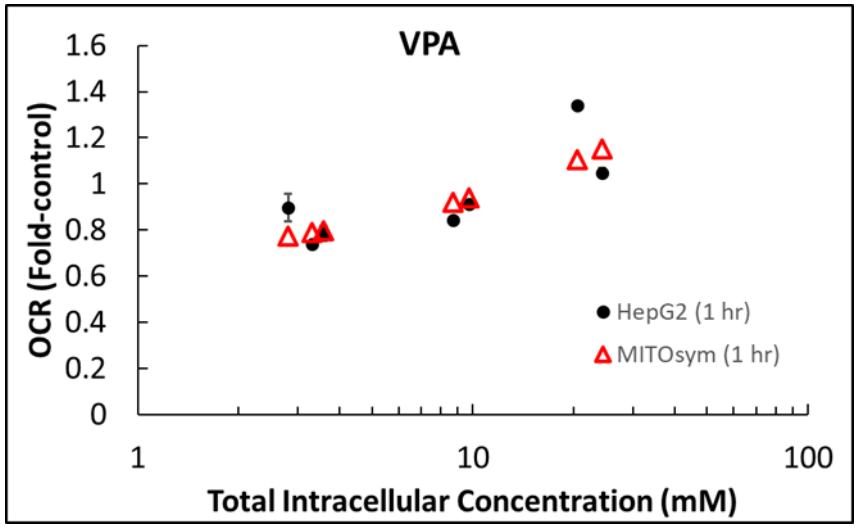
Taylor 2018

1500 mg BID

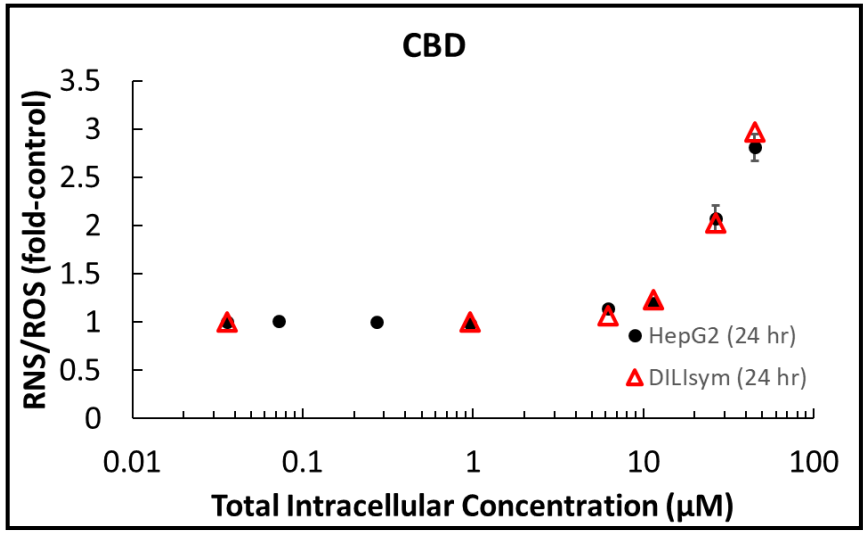
Parameterization of Hepatotoxicity Mechanisms for Both Compounds was Based on *in vitro* Assay Results

- Mechanistic *in vitro* data were collected for VPA, CBD, and its two main plasma metabolites (7-COOH-CBD, 7-OH-CBD) for three hepatotoxicity mechanisms: production of reactive oxygen stress (ROS), mitochondrial dysfunction, and inhibition of bile acid (BA) transporters
  - The *in vitro* data were used to determine toxicity parameter values for each compound in DILIsym

Assay Evaluating Mitochondrial Toxicity (example: VPA)



Assay Evaluating Reactive Oxygen Stress Toxicity (example: CBD)



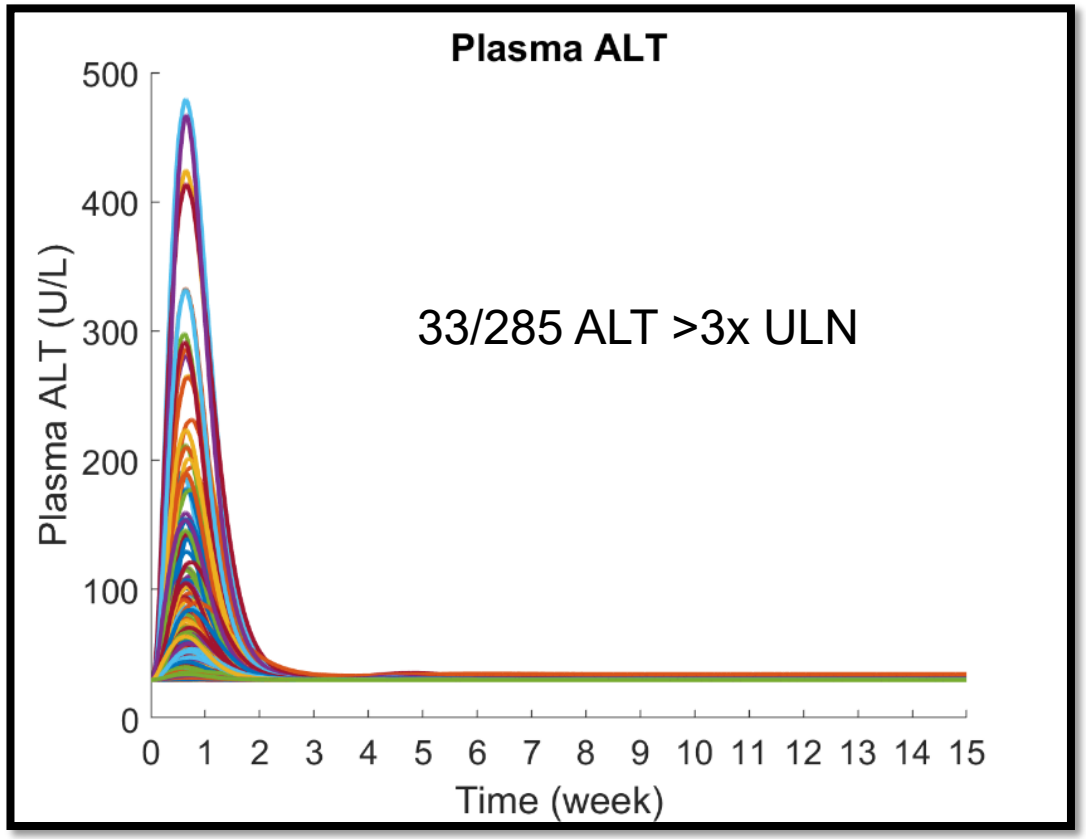
VPA Simulations in DILIsym Accurately Predict Frequency and Dynamics of ALT Elevations Observed Clinically

- Simulations of VPA for 15 weeks with dose titration
  - 1st week: 5 mg/kg BID
  - 2nd week: 10 mg/kg BID
  - maintenance dose: 10 mg/kg BID

- Simulations with the mitochondrial biogenesis mechanism show resolution of ALT elevations with continued dosing, which matches clinical observations

- Simulated frequency of ALT elevations (12%) matches clinical observations (5 – 10%) [NIH LiverTox Website]

VPA Titrated to 10 mg/kg BID



DILIsym CBD Simulation Results Predict an Exposure-Response Relationship with ALT Elevations

CBD Dose	ALT > 3x ULN
12.5 mg/kg BID Fasted	2/285 (0.7%)
12.5 mg/kg BID Fed	149/285 (52.3%)
10 mg/kg BID Fed	108/285 (37.9%)
5 mg/kg BID Fed	24/285 (8.4%)

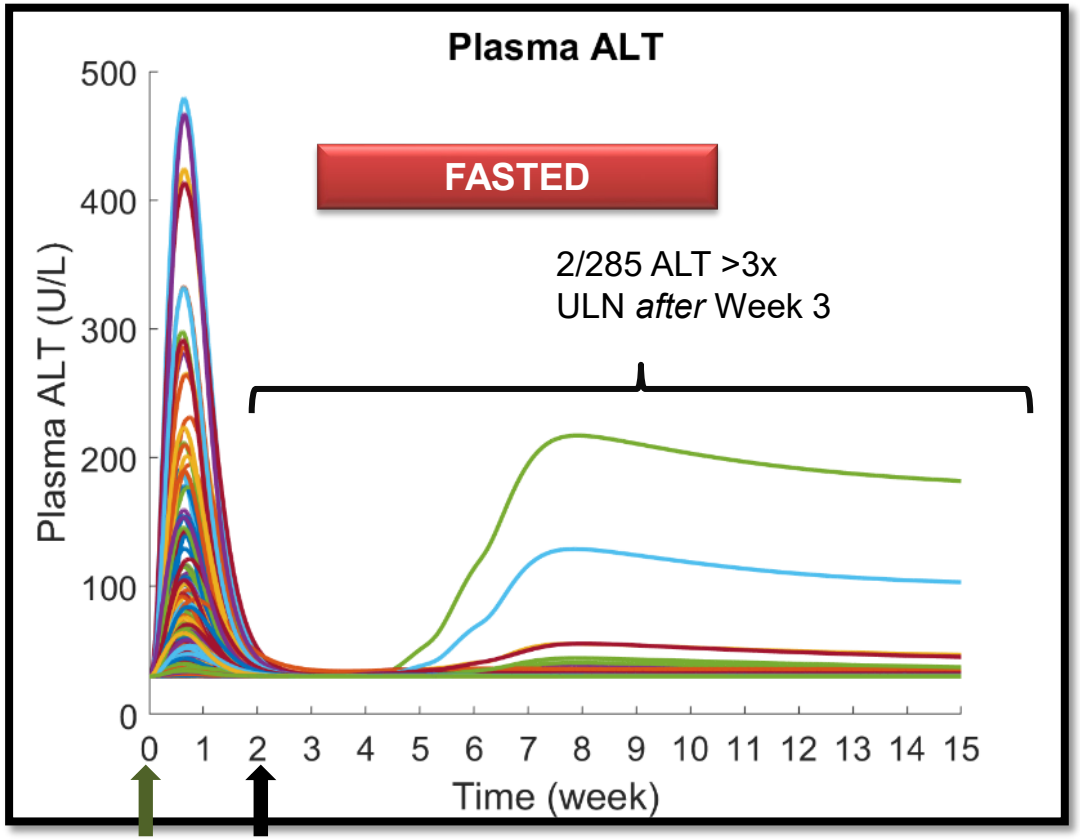
In a trial of 16 healthy adults receiving 1500 mg/day CBD (fed state), 7 (44%) developed ALT elevations >3x ULN

[Watkins et. al. 2020]

- Simulations of CBD for 15 weeks with dose titration
  - 1st week: 2.5 mg/kg BID
  - Increase by 2.5 mg/kg BID weekly until maintenance dose reached
- Doses are simulated under entirely "Fasted" or entirely "Fed" conditions
- Simulations predict exposure-dependent ALT elevations
  - Note: the exposure under "Fed" condition is about 5x higher than under "Fasted" condition for the same dose

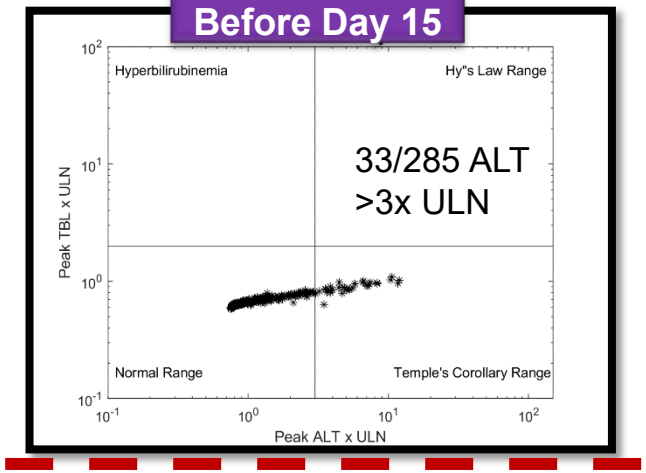
VPA and CBD Combined Therapy Shows Two Separate Peaks in Simulated ALT

- VPA + CBD concomitant dosing simulated for 15 weeks in DILIsym
- VPA dosed alone for first two weeks; titrated (as outlined before) up to 10 mg/kg BID maintenance dose
- Beginning on 3rd week, CBD was titrated up to 12.5 mg/kg BID
  - Maintenance dose reached starting 7th week
  - All CBD doses were under “Fasted” condition
- Simulated ALT elevations had returned to near baseline levels before CBD dosing began
- After CBD dosing began, a second (less frequent) elevation in ALT levels was predicted

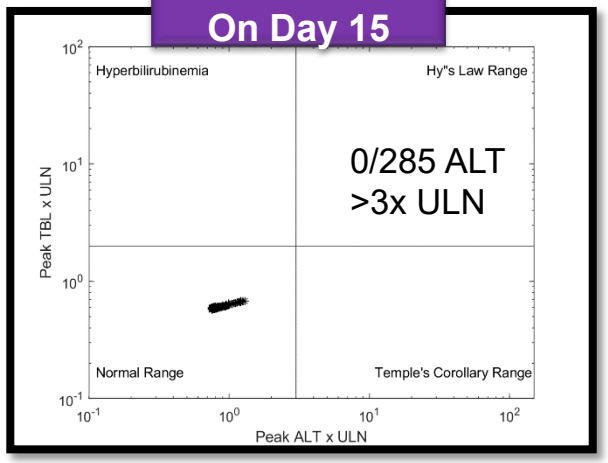


When CBD is Given After VPA Maintenance Achieved, Simulated Toxicity Effects Appear Additive

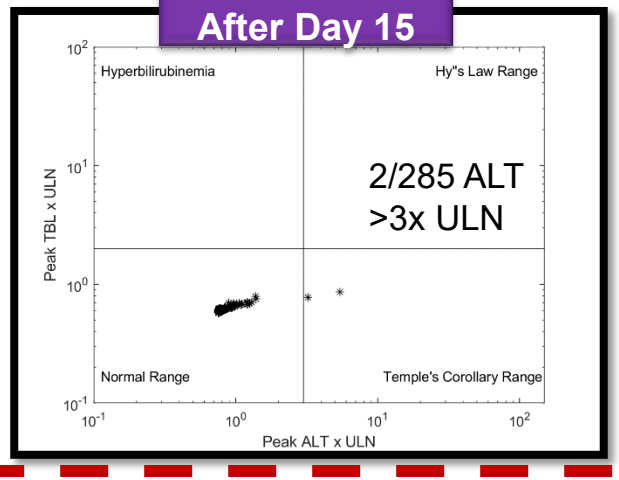
VPA + CBD Before Day 15

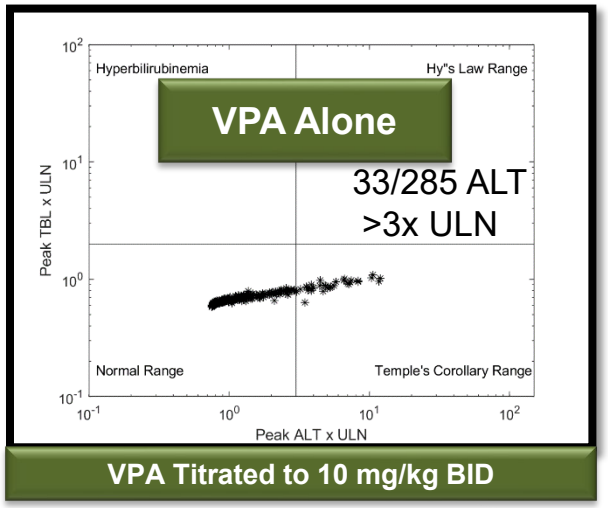


VPA + CBD On Day 15

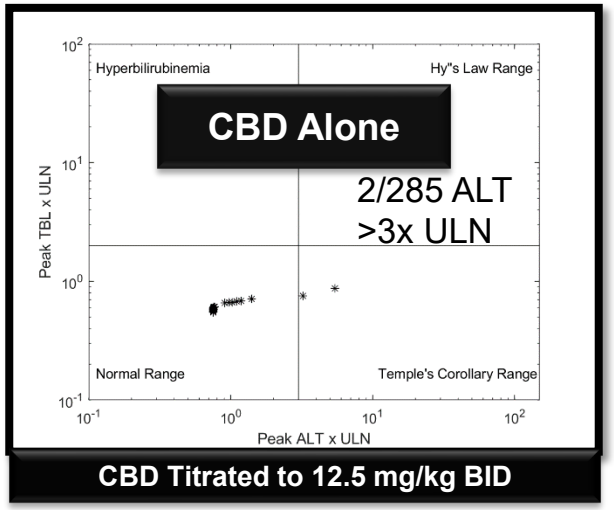


VPA + CBD After Day 15





- **Combined therapy results** are shown above the dashed line
- Individual therapy results are reprinted below the dashed line for comparison
- By end of 2nd week, the ALT and bilirubin levels are nearly back to ULN levels



Mechanistic Investigations in SimCohorts Indicate Strong Sensitivity to Oxidative Stress

- Mechanistic analyses performed using n=46 lowest body weight SimCohort
  - CBD maintenance dose 12.5 mg/kg BID under “Fed” conditions
- Toxicity does not manifest if ROS is turned off
- Parent CBD has largest contribution to simulated ALT elevations
  - Metabolites also contribute to simulated toxicity

Mechanisms Off*	Chemical Species Off**	ALT >3x ULN
None	None	24/46
ROS	None	0/46
ETCi	None	24/46
BAi	None	24/46
None	CBD	11/46
None	7-COOH-CBD	16/46
None	7-OH-CBD	23/46

*Mechanisms Off refers to mechanisms that were disabled during the simulation
**Chemical Species Off refers to drug/metabolite species whose toxicity was disabled during the simulation

DILIsym Simulation Results Summary

Compound	Dose	ALT > 3x ULN
VPA Alone	10 mg/kg BID	33/285 (11.6%)
CBD Alone	12.5 mg/kg BID Fasted	2/285 (0.7%)
	12.5 mg/kg BID Fed	149/285 (52.3%)
	10 mg/kg BID Fed	108/285 (37.9%)
	5 mg/kg BID Fed	24/285 (8.4%)
VPA + CBD	10 mg/kg BID (VPA) 12.5 mg/kg BID Fasted (CBD)	35/285 (12.3%)

- Simulation results show an exposure-response relationship between CBD and frequency of ALT elevations
- The DILIsym simulations suggest that interference with mitochondrial respiration does not account for the large increase in frequency of ALT elevations observed in VPA-treated patients who start treatment with CBD