Verdiperstat Is a Drug Candidate in Clinical Trials for a Rare Neurological Disorder

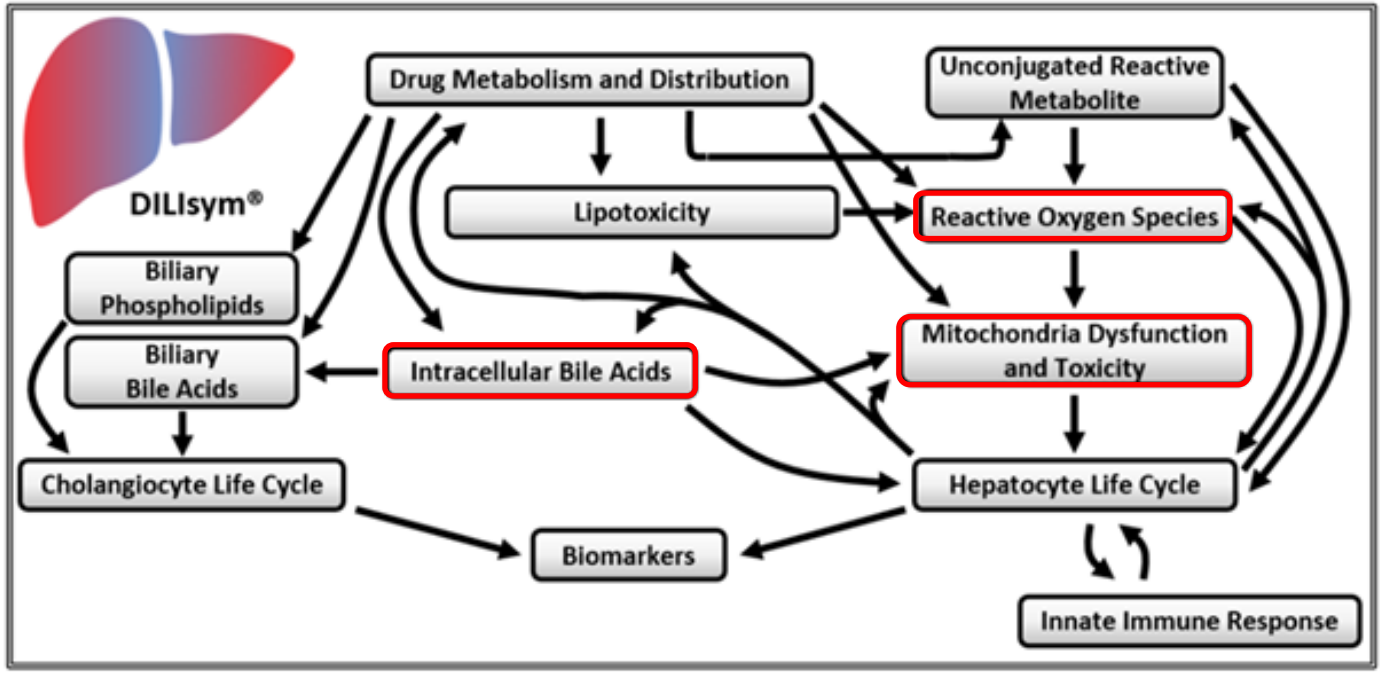
- Verdiperstat is a first-in-class myeloperoxidase inhibitor for the treatment of multiple system atrophy (MSA) and amyotrophic lateral sclerosis (ALS)
- Phase 2 trials showed potential for efficacy at 600 mg BID dose
- Biohaven wanted to analyze liver safety of verdiperstat before proceeding to Phase 3
  - High-dose drug with some *in vitro* signals
  - Had prior success utilizing DILIsym for programs

Verdiperstat Project Executive Summary

- **DILIsym simulations of verdiperstat with mechanistic toxicity parameters predicted no ALT elevations > 3X ULN at doses up to 600 mg BID**
  - No hepatotoxicity was predicted with 600 mg BID verdiperstat for 48 weeks with the primary DILIsym parameterization
  - No hepatotoxicity (ALT > 3X ULN) was predicted with 600 mg BID verdiperstat for 48 weeks with the alternate, most conservative DILIsym parameterization and the *worse-case scenario* of highest population verdiperstat exposure coupled with the most sensitive simulated patient
    - Most extreme, worse-case scenario did result in single ALT > 2X ULN, so ALT elevations from verdiperstat are predicted to be possible, but rare and mild
- *In vitro* mechanistic DILI assays performed
  - Bile acid transporter inhibition, mitochondrial toxicity, and oxidative stress (ROS) observed at very high concentrations
- Physiologically-based pharmacokinetic (PBPK) modeling of verdiperstat was successfully completed within GastroPlus software
  - Clinical PK data were used to optimize and validate the PBPK representation
  - Inter-individual PK variability observed from clinical trials was adequately recapitulated in population simulations

In Vitro Data Indicates that Verdiperstat Elicits Possible Signals for Bile Acid Transporter Inhibition, Mitochondrial Dysfunction, and Oxidative Stress

- DILIsym represents 3 distinct mechanisms of toxicity
- *In Vitro* data were gathered to evaluate effects related to 3 DILI mechanisms
- Mitochondrial toxicity signals and oxidative stress signals observed
- Bile acid transport inhibition effect observed through MRP4 inhibition signal

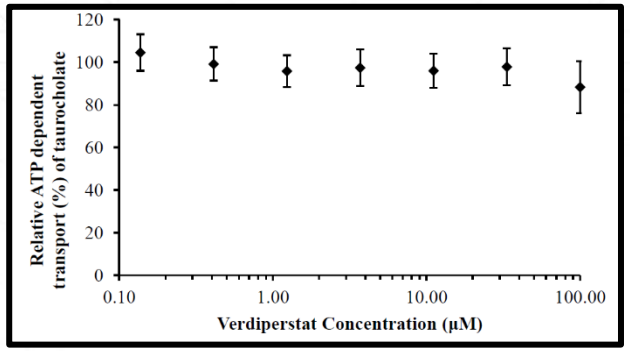


Compound	BA Transport signals	Mitochondrial dysfunction signals	Oxidative stress signals
Verdiperstat	Yes	Yes	Yes

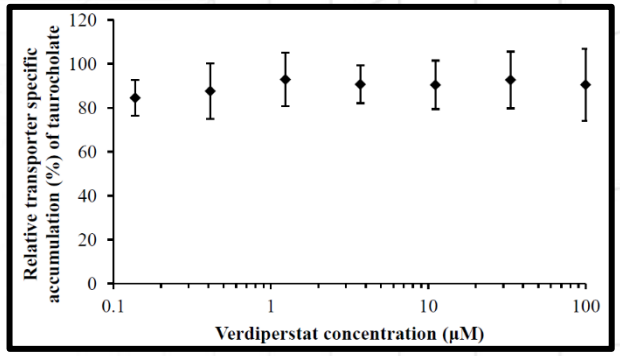
Bile Acid Transporter Inhibition Studies Suggest Verdiperstat-Mediated Bile Acid Effects

- Bile acid transporters inhibition studies reveal that verdiperstat has no inhibition effect on BSEP, NTCP and MRP3 transporters
- Verdiperstat-mediated bile acid effects are possible due to moderate MRP4 inhibition at very high concentrations

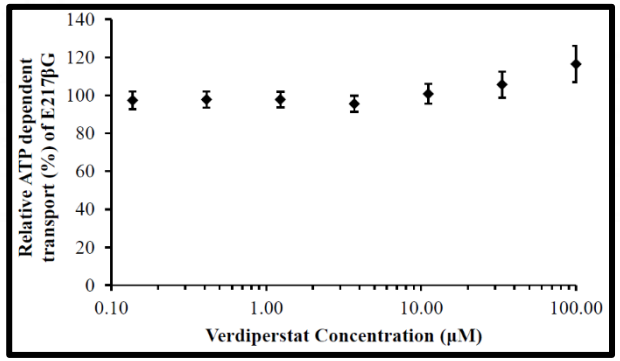
BSEP **No inhibition**



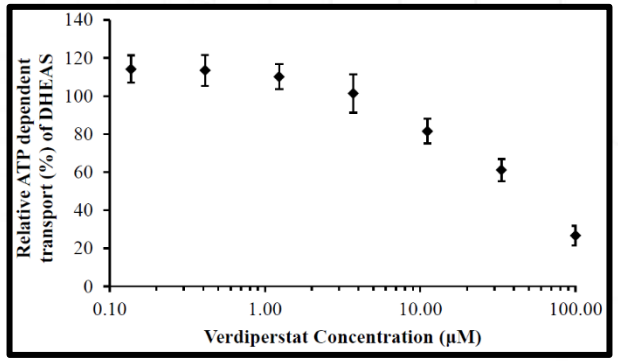
NTCP **No inhibition**



MRP3 **No inhibition**

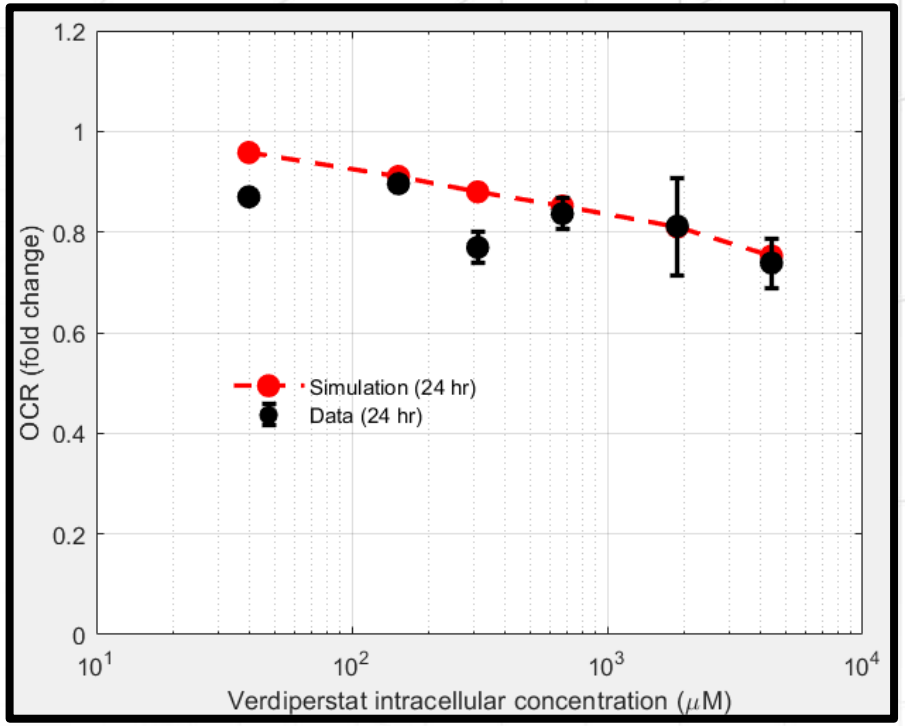


MRP4 **Estimated IC_{50} 32.55 µM**
73.4% inhibition at 100 µM



MITOsym was Used to Determine Mitochondrial Toxicity Parameters for Verdiperstat

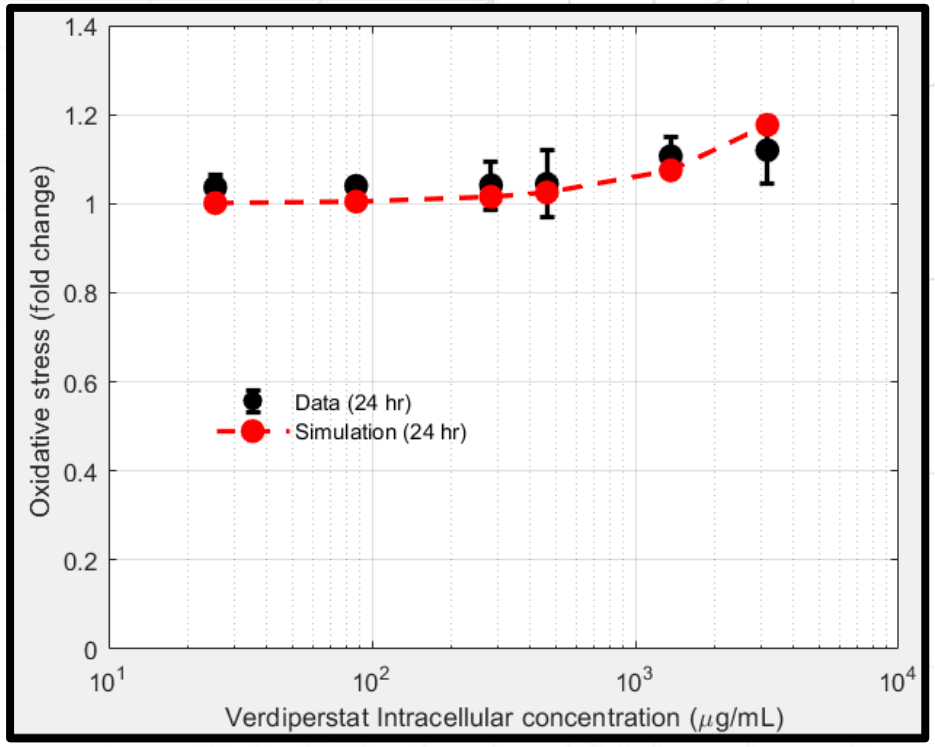
- Verdiperstat mediated mitochondrial dysfunction assayed using the Agilent Seahorse XF Analyzer
  - Oxygen consumption rate (OCR) was normalized to vehicle control and cell count
  - 24 hr data plotted against intracellular verdiperstat concentrations
  - Intracellular concentrations were estimated from lysate measures by LC/MS
- Concentration-dependent changes in OCR were recapitulated in MITOsym
  - MITOsym was employed to parameterize ETC inhibition of verdiperstat
  - 24 hr OCR data was optimized using ETC 1 and ETC 3 inhibition mechanisms
  - Model closely recapitulates observed OCR fold changes, with few exceptions
- MITOsym parameters were translated to DILIsym using a scaling factor obtained from exemplar compounds



Software Parameter	MITOsym value	DILIsym value
Coefficient for ETC Inhibition 1	20 mM	6.94 x 10^5 uM
Coefficient for ETC Inhibition 3	0.007 mM	243 uM
Max inhibitory effect for ETC inhibition 3	0.78	0.39

DILIsym Parameters were Identified for Verdiperstat-Mediated Oxidative Stress

- High content screening assay following 6 or 24 hr incubation with HepG2 cells shows very mild verdiperstat-mediated oxidative stress elevation at the highest concentrations
  - 24 hr HCS data was used for oxidative stress (RNS/ROS) parametrization in DILIsym
  - 24 hr data plotted against intracellular verdiperstat concentrations
  - Intracellular concentrations were estimated from lysate measures by LC/MS
- Dose-dependent changes in RNS/ROS were recapitulated in DILIsym
  - Optimized liver RNS/ROS parameters in DILIsym to closely recapitulate observed changes of verdiperstat-mediated oxidative stress in HCS data



DILIsym Parameter	DILIsym parameter values	Units
Liver RNS/ROS production rate Constant 1	1.15×10^{-6}	mL/nmol/hour

DILIsym Toxicity Parameters for Verdiperstat

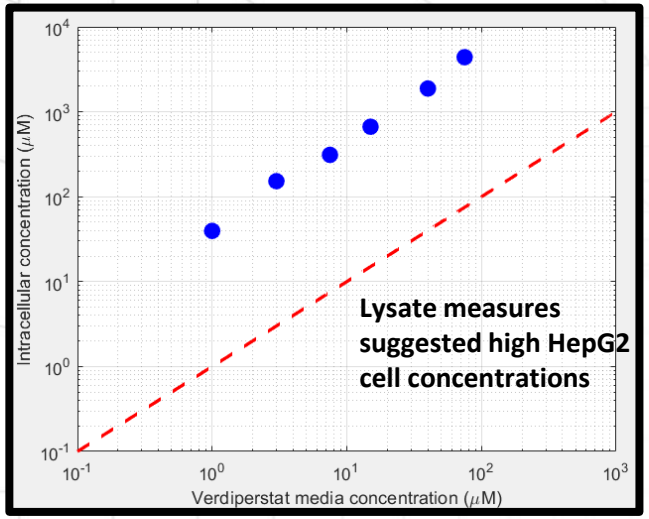
Mechanism	DILIsym Parameter	Unit	Primary Verdiperstat Value*
BA Transport Inhibition	Inhibition constant for BSEP	µM	No inhibition
	Inhibition constant for basolateral efflux (MRP3/4)	µM	32.55**
	Inhibition constant for NTCP	µM	No Inhibition
Oxidative Stress	Liver RNS/ROS production rate constant 1	mL/nmol/hour	1.15×10^{-6}
Mitochondrial Dysfunction	Coefficient for ETC Inhibition 1	µM	6.94×10^{5}
	Coefficient for ETC Inhibition 3	µM	243
	Max inhibitory effect for ETC inhibition 3	Dimensionless	0.39

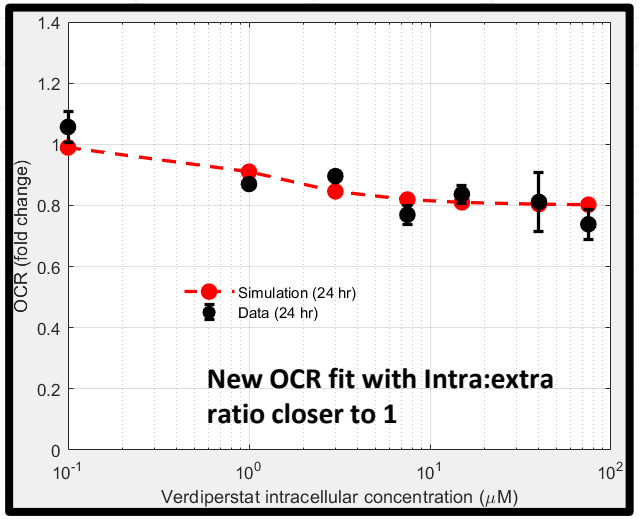
* Values shown in the table for DILIsym input parameters should not be interpreted in isolation with respect to clinical implications, but rather, should be combined with exposure in DILIsym to produce simulations that have predictive and insightful value

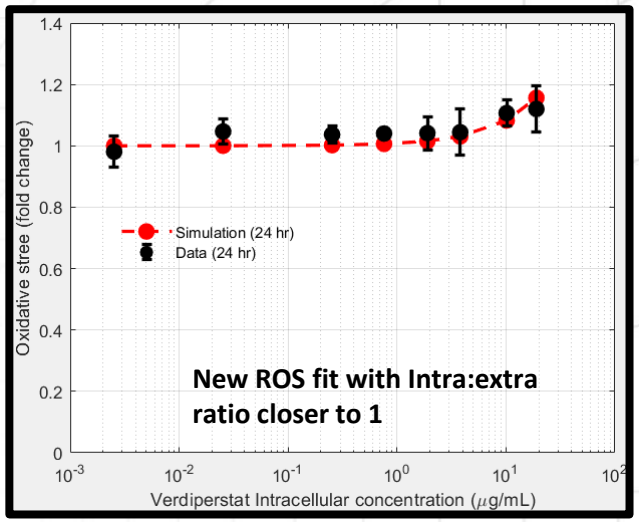
** Mixed inhibition with alpha = 5 assumed

Primary Parameterization

Alternative Toxicity Parameters were Identified for Verdiperstat Based on Estimated Kp,liver







- LC/MS data showed significant verdiperstat accumulation in cells, suggesting high Kp,liver values; PBPK model and physicochemical properties suggested Kp,liver closer to 1
- Sensitivity analysis performed using Kp,liver = 1 to assess verdiperstat toxicity responses
  - Intracellular concentration was determined using Kp,liver = 1
  - 24 hr OCR data was optimized using MITOsym based on ETC 1 and ETC 3 inhibition mechanisms; MITOsym parameters translated to DILIsym using scaling factors
  - 24 hr HCI data was used for oxidative stress (RNS/ROS) parametrization in DILIsym

Alternate Parameterization

Alternative DILIsym Toxicity Parameters of Verdiperstat for Sensitivity Analysis

Mechanism	DILIsym Parameter	Unit	Alternate Verdiperstat Value*	Primary Verdiperstat Value*
BA Transport Inhibition	Inhibition constant for BSEP	µM	No inhibition	No inhibition
	Inhibition constant for basolateral efflux (MRP3/4)	µM	32.55**	32.55**
	Inhibition constant for NTCP	µM	No Inhibition	No Inhibition
Oxidative Stress	Liver RNS/ROS production rate constant 1	mL/nmol/hour	**1.7×10^{-4}**	1.15×10^{-6}
Mitochondrial Dysfunction	Coefficient for ETC Inhibition 1	µM	6.94×10^{5}	6.94×10^{5}
	Coefficient for ETC Inhibition 3	µM	**2.43**	243
	Max inhibitory effect for ETC inhibition 3	Dimensionless	0.39	0.39

* Values shown in the table for DILIsym input parameters should not be interpreted in isolation with respect to clinical implications, but rather, should be combined with exposure in DILIsym to produce simulations that have predictive and insightful value

** Mixed inhibition with alpha = 5 assumed

Alternate Parameterization

DILIsym Simulations Show No Liver Toxicity at Any Dose for Verdiperstat

- Clinical protocols simulated for verdiperstat
  - Phase 1: 50 and 100 mg BID, 10 days
    - Mild liver enzyme elevations observed in clinic
  - Phase 3: 300 mg BID, 12 weeks
  - Phase 3: 600 mg BID, 48 weeks
- ***No simulated ALT elevations >3X ULN observed for any simulated dose with primary DILIsym parameters***

Dosing Protocol	ALT >3X ULN*, Primary Parameterization
50 mg BID, 10 days	0/285**
100 mg BID, 10 days	0/285
300 mg BID, 12 weeks	0/285
600 mg BID, 48 weeks	0/285

**Upper limit of normal (ULN) in DILIsym is 40 U/L*

***The full v8-1 SimPops (n=285) of normal healthy volunteers was used, with verdiperstat PK variability incorporated from the GastroPlus PBPK model*

Primary Parameterization

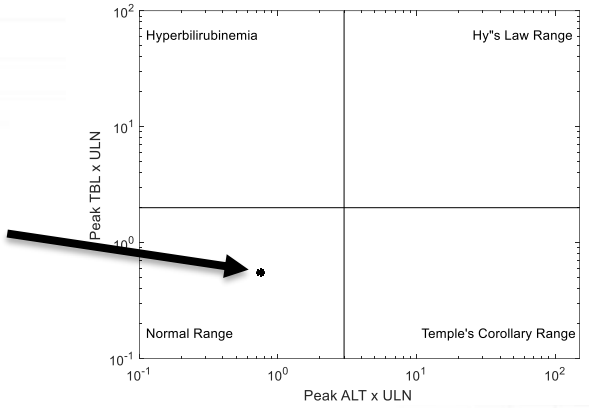
Verdiperstat Primary DILIsym Parameterization Shows No Liver Signals

- No change in ALT or bilirubin observed at any simulated dose using primary DILIsym parameterization
  - All 285 patients are stacked on top of one another, so they appear as a single dot

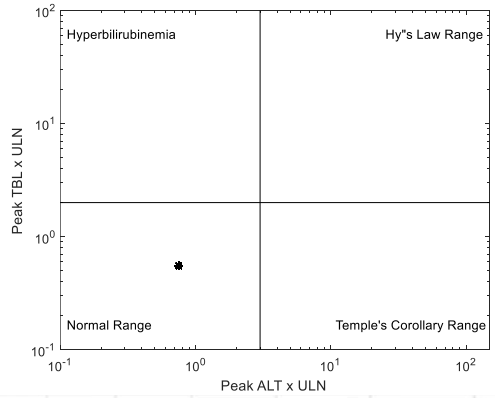
- ***Verdiperstat, based on DILIsym mechanisms and most trusted parameterization techniques of DILIsym Services team, appears to be unlikely to cause DILI***

Primary Parameterization

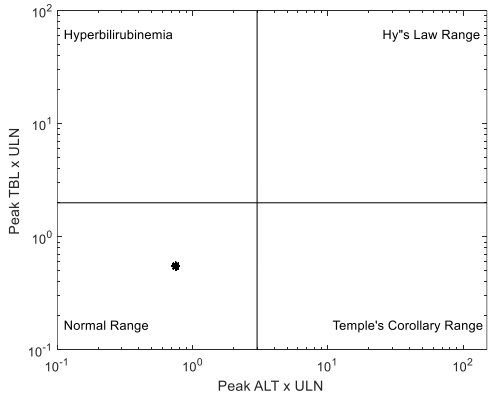
50 mg BID, 10 days



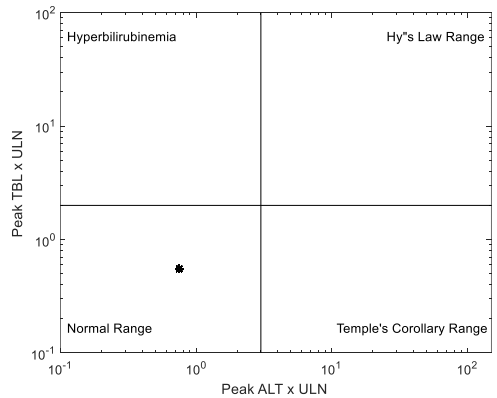
100 mg BID, 10 days



300 mg BID, 12 weeks



600 mg BID, 48 weeks

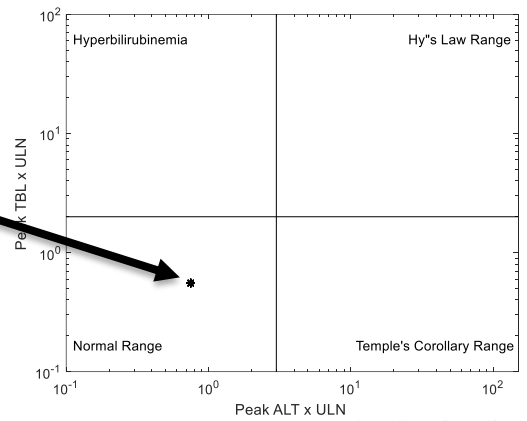


Verdiperstat Alternate Parameterization Shows One Mild ALT Elevation At 600 mg BID Dose

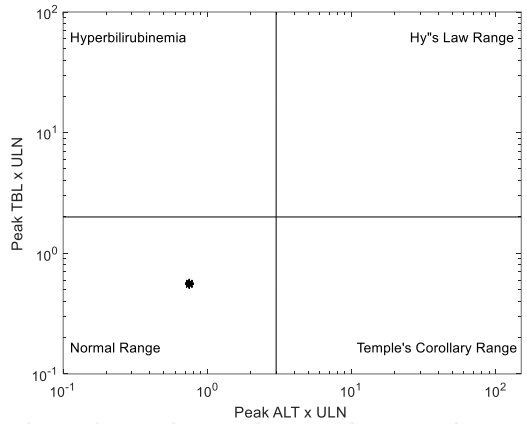
- No significant elevations (> 2X ULN) in ALT or bilirubin observed at any doses using alternative DILIsym parameterization
  - All 285 patients are stacked on top of one another, so they appear as a single dot
- Mild (~ULN) ALT increase observed at 600 mg dose using alternate parameterization
  - Mild elevation due to mild ETC inhibition (mito) effect of drug
- ***Verdiperstat, based on DILIsym mechanisms and conservative parameterization technique of DILIsym Services team, appears to be unlikely to cause DILI but shows rare, mild signals at high doses***

Alternate Parameterization

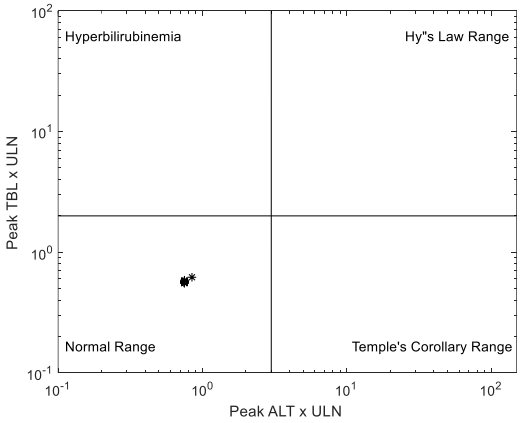
50 mg BID, 10 days



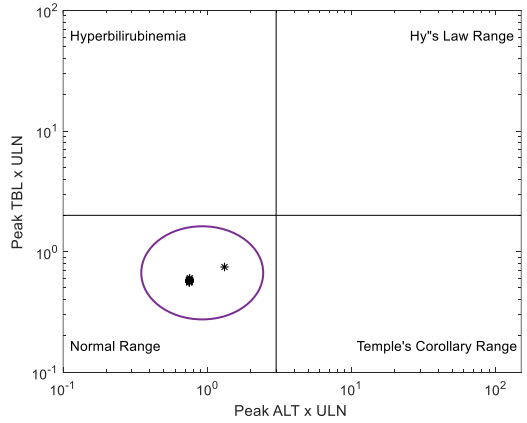
100 mg BID, 10 days



300 mg BID, 12 weeks



600 mg BID, 48 weeks



Verdiperstat Shown to be Safe in Phase 3 Clinical Trial

- After simulation work was completed, verdiperstat underwent a Phase 3 clinical trial for MSA
- No significant liver signal was observed
- Verdiperstat did not show efficacy on its target above placebo and was not advanced further for MSA
- Phase 3 study in ALS is ongoing

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BIOHAVEN PROVIDES UPDATE ON PHASE 3 TRIAL AND MULTIPLE SYSTEM ATROPHY (MSA) PROGRAM

09/27/2021

NEW HAVEN, Conn., Sept. 27, 2021 /PRNewswire/ -- Biohaven Pharmaceutical Holding Company Ltd. (NYSE: BHVN) today announced results from a focused analysis of a clinical trial of verdiperstat in multiple system atrophy (MSA). Verdiperstat did not statistically differentiate from placebo on the prespecified primary efficacy measure, nor on the key secondary efficacy measures. Initial analysis of safety data was consistent with the overall profile of verdiperstat from prior clinical trial experience. Additional analyses are still pending, and full study results will be presented at an upcoming scientific meeting.

biohaven pharmaceuticals

Irfan Qureshi, M.D., Vice President of Neurology at Biohaven commented, "While we are disappointed that verdiperstat did not demonstrate efficacy for the treatment of MSA, Biohaven remains committed to fighting on behalf of people living with neurodegenerative diseases. There are currently no approved disease modifying therapies for MSA and we must continue to advance the science to improve treatment outcomes for patients suffering from this disease. We are extremely grateful to the international MSA community – especially the patients and their families, investigators and their teams, and patient advocacy groups – who made the trial possible."