VTX2735: A Potent, Selective NLRP3 Inhibitor with Disease-Modifying Effects in CAPS Patients

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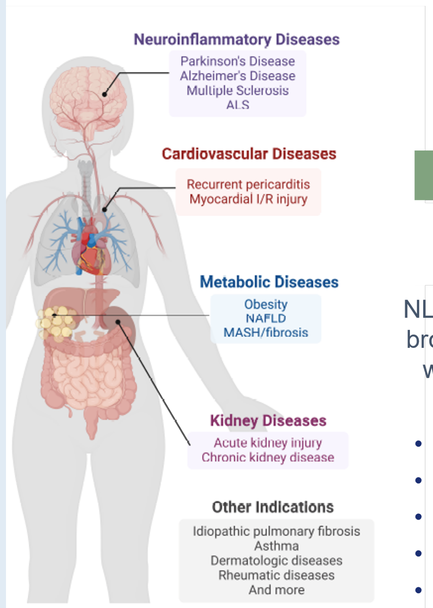
Abstract

VTX2735 is a novel, potent and selective small-molecule inhibitor of wild-type NLRP3 and NLRP3 bearing common mutations associated with Cryopyrin-Associated Periodic Syndrome (CAPS). We will present the discovery of VTX2735 and its characterization through the recently completed Phase 2a study in CAPS patients.

VTX2735 potently inhibits wild-type NLRP3 in human monocytes (IC_{50} of 2 nM), major NLRP3 variants in CAPS patients' monocytes (IC_{50} between 14-166 nM), and IL-1b release induced by LPS/ATP in a human whole blood assay (IC_{50} of 60 nM). *In vivo*, VTX2735 is active in mice challenged with LPS/ATP (ED_{50} of 0.2 mg/kg) and in a gouty rat model. VTX2735 is a BCS Class I compound, with excellent pre-clinical ADME attributes and high oral exposures in all species studied (mouse, rat, dog, monkey, human). The compound is peripherally restricted and does not permeate the blood-brain barrier. VTX2735 is well tolerated in humans and long-term toxicology studies support the efficacious human exposures.

In patients with CAPS, VTX2735 demonstrated durable target engagement that ameliorated the CAPS key symptom score, improved patient well-being and resolved elevated inflammatory markers. This evidence supports the use of VTX2735 in CAPS and other diseases driven by aberrant IL-1b

Ventyx NLRP3 Pipeline



Ventyx NLRP3 Inhibitors

VTX2735

Peripheral NLRP3 Inhibition with Strong Phase 2 Data

NLRP3 inhibition has therapeutic potential in a broad range of systemic diseases, particularly where IL-1β antibodies have demonstrated therapeutic benefit

- **Biologic-like efficacy in CAPS (FCAS)**
- Highly potent and selective
- Robust, dose-dependent PD effects
- Well-tolerated in Ph1 and Ph2
- Opportunities in RP, MACE, HS

VTX3232

Potent CNS Penetrant NLRP3 Inhibition

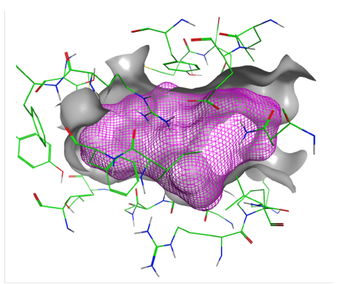
NLRP3 activation (inhibition) has been linked to a range of neuroinflammatory and neurodegenerative conditions with high unmet medical need

- Highly potent and selective
- Robust, dose-dependent PD effects
- Outstanding CNS coverage at multiple doses
- Well-tolerated in healthy volunteers
- Parkinson's, CV/Metabolic studies in startup

VTX2735: Discovery and Pre-Clinical Studies

Final Lead Optimization

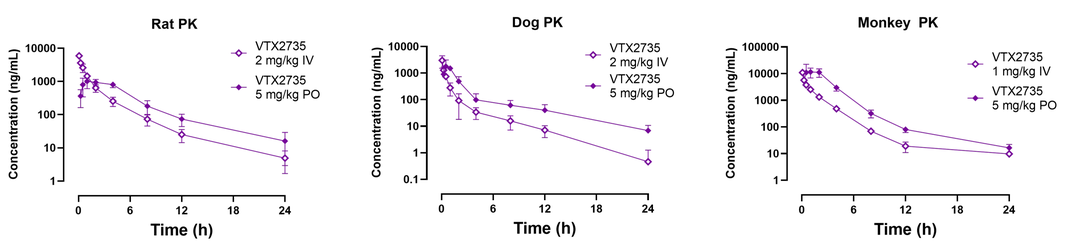
> 100 compounds prepared



	NLRP3 Binding K_D(nM)	Hu Whole Blood IL-1β Release IC_{50} (nM)
VTX2735	**< 1**	**80**
MCC950	150	400

- VTX2735 potently and reversibly binds to the proximal NLRP3 Walker B motif and inhibits NLRP3 ATPase activity
- No inhibition of other inflammasomes
- Binding kinetics and physical properties translate to highly potent whole blood activity and suitable preclinical PK profile
- No CYP inhibition, induction, or TDI
- No hERG inhibition; not genotoxic/ mutagenic
- High safety margins from 28d tox studies in rat, cyno

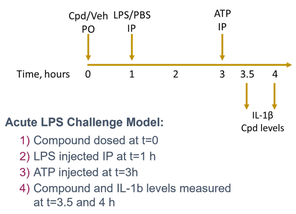
In Vivo PK in Preclinical Species



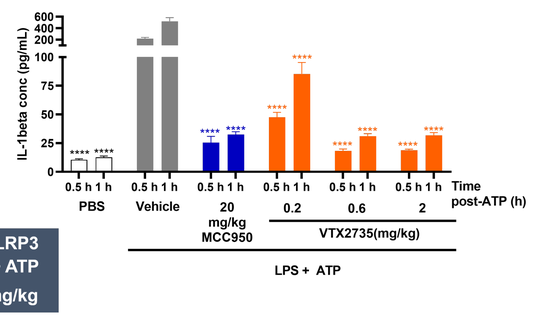
	Dose	$t_{1/2}$ (hr)	CL (mL/min/kg)	V_{ss} (L/kg)	Cmax (ng/mL)	AUC (ng/mL*hr)	AUC/ Dose	%F
Rat PK	2 mg/kg (IV)	4.2	5.6	0.70	7590	6113	3056	-
	5 mg/kg (PO)	4.8	-	-	1037	6374	1275	**42**
Dog PK	2 mg/kg (IV)	3.7	20	1.8	4795	1674	837	-
	5 mg/kg (PO)	5.2	-	-	2060	3651	730	**85**
Cyno PK	1 mg/kg (IV)	3.3	1.6	1.8	15265	10413	10413	-
	5 mg/kg (PO)	4.1	-	-	16867	41800	8360	**80**

VTX2735 is well absorbed with high bioavailability in preclinical species

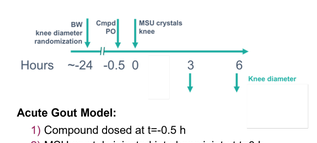
In Vivo Efficacy in Preclinical Species



Acute LPS Challenge Model:
1) Compound dosed at t=0
2) LPS injected IP at t=1 h
3) ATP injected at t=3h
4) Compound and IL-1b levels measured at t=3.5 and 4 h

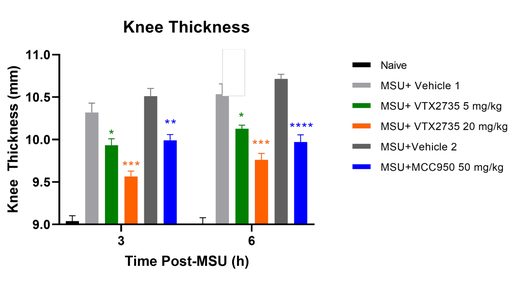


VTX2735 is a potent inhibitor of NLRP3 function after challenge with LPS+ ATP
Dose responsive with ED_{50} < 0.2 mg/kg

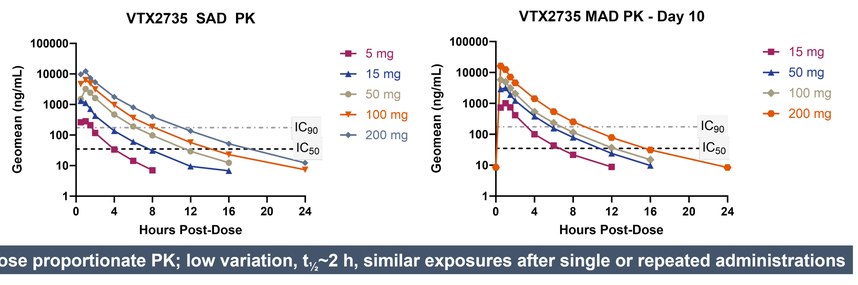


Acute Gout Model:
1) Compound dosed at t=-0.5 h
2) MSU crystals injected into knee joint at t=0 h
3) Knee diameter measured at t=3 and 6 h

VTX2735 is a potent inhibitor of NLRP3 function after challenge with intra-articular crystals
Dose related with ED_{50} ~ 20 mg/kg; greater in vivo potency than MCC950

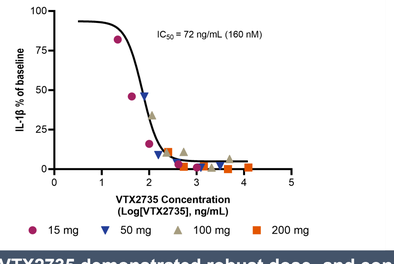


VTX2735 Phase 1 SAD/MAD Study

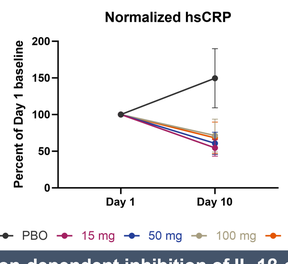


Dose proportionate PK; low variation, $t_{½}$~2 h, similar exposures after single or repeated administrations

Concentration-Dependent Suppression of IL-1β *Ex Vivo*



Strong Inhibition of High Sensitivity CRP (hsCRP)



VTX2735 demonstrated robust dose- and concentration-dependent inhibition of IL-1β *ex vivo*
Statistically significant inhibition of normalized hsCRP at all 4 doses (cardiovascular risk factor)

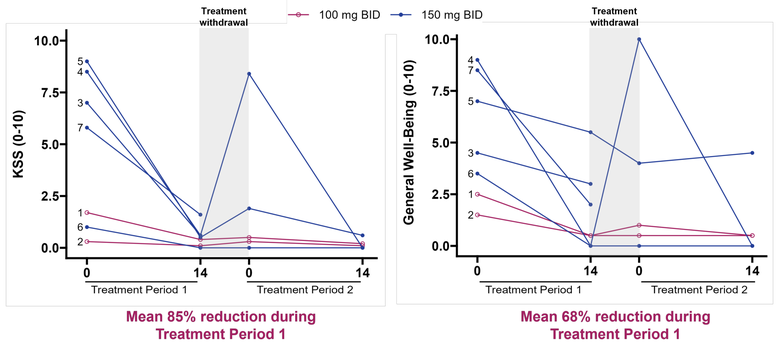
VTX2735 Phase 2 CAPS (FCAS) Trial Results

IC_{50} in Blood Monocyte Assay (nM)

CPD	Challenge	FCAS1 L353P	FCAS2 L353P	FCAS3 L353P	FCAS4 A439V/G564R	FCAS.MWS E525K/V198M	NOMID F309Y
		75% of all CAPS patients In North America					**Most Severe**
VTX2735	LPS	117	56	166	14	24	17
MCC950	LPS	>10K	>10K	>10K	1,264	>10K	>10K

Key Symptom Score (0-10)*
Daily mean of five symptom scores

General Well-Being (0-10)*
"Considering all the ways FCAS affects you, please rate how you are doing"



Mean 85% reduction during Treatment Period 1

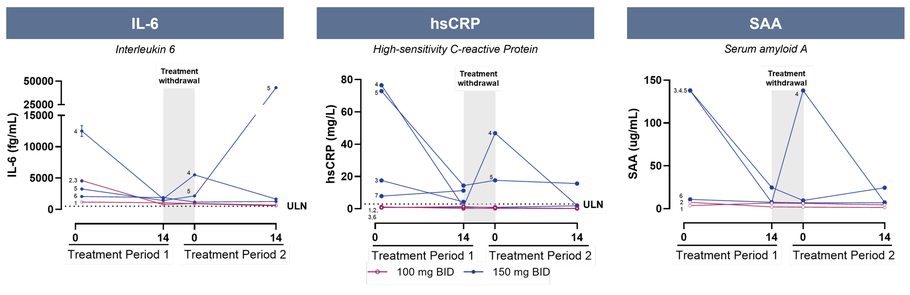
Mean 68% reduction during Treatment Period 1

Reductions in IL-6, hsCRP and SAA Observed as Expected with NLRP3 Inhibition

IL-6
Interleukin 6

hsCRP
High-sensitivity C-reactive Protein

SAA
Serum amyloid A



Clinical Proof of Concept Achieved in CAPS Patients

VTX2735 showed clinically-meaningful effects on disease activity and relevant biomarkers

Dr. Hal Hoffman (UCSD): "Results similar to what we have seen in IL-1 inhibition studies"

VTX2735 was well-tolerated; all adverse events were mild or moderate and resolved without treatment interruption