



Corporate Presentation  
Fourth Quarter 2021

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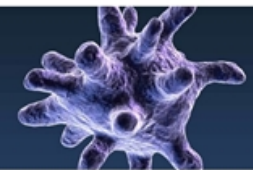
VTX958  
PHASE 1

VTX002  
PHASE 2 READY

VTX2735  
PHASE 1

CNS NLRP3  
PRECLINICAL

SUMMARY  
MILESTONES & HIGHLIGHTS



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BIOSCIENCES

## Our Leadership Team

### Management



**Martin Auster, MD**  
CHIEF FINANCIAL OFFICER



**John Nuss, PhD**  
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**Raju Mohan, PhD**  
CHIEF EXECUTIVE OFFICER, FOUNDER



**Chris Krueger, JD**  
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**Jörn Drappa, MD, PhD**  
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**Jigar Choksey**  
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**Somu Subramaniam**  
MANAGING PARTNER, NEW  
SCIENCE VENTURES

**William White**  
CHIEF FINANCIAL OFFICER,  
AKERO THERAPEUTICS

## Our Mission: To become a Leading Immunology Company

Underpinned by strong drug discovery and development capabilities



### With three, differentiated, clinical-stage candidates

and a deep pipeline of preclinical programs that target immune-mediated and inflammatory disease indications



### Our internally-discovered small molecule drugs

allow us to own 100% commercial rights to our entire portfolio with long patent lives for all product candidates

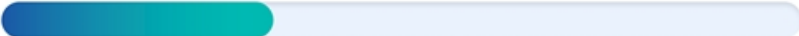

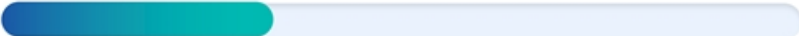
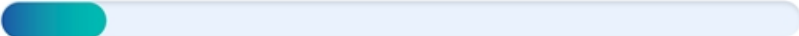


### Our experienced team and our internal R&D engine

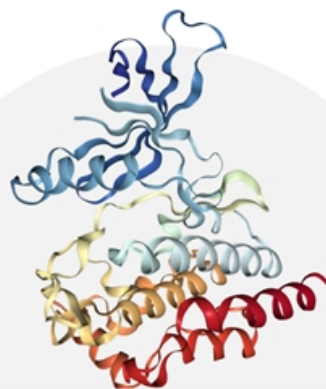
continue to generate candidates with potential to address diseases with high unmet need

## Broad Pipeline of Candidates With Multiple Near-Term Catalysts

Addressing Established Inflammatory and Immunology Markets with Wholly Owned Product Portfolio

TARGET	PROGRAM	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	NEXT ANTICIPATED MILESTONES
<b>TYK2</b>	VTX958		Potential indications include psoriasis, psoriatic arthritis, Crohn's disease and others			Complete Phase 1 MAD H1 2022 Initiate Phase 2 POC trial(s) H2 2022
<b>S1P1R</b>	VTX002		Ulcerative Colitis			Initiate Phase 2 trial Q4 2021 Report topline Phase 2 data 2023
<b>NLRP3</b> <i>Peripheral</i>	VTX2735		Potential indications include cardiovascular, hepatic, renal, and rheumatologic diseases			Complete Phase 1 H1 2022 Initiate Phase 2 POC trial(s) H2 2022
<b>NLRP3</b> <i>CNS-penetrant</i>	Discovery		Neuroinflammatory diseases			Select lead candidate Q4 2021 File IND H2 2022





Orally Bioavailable,  
Selective Allosteric  
Inhibitor of TYK2

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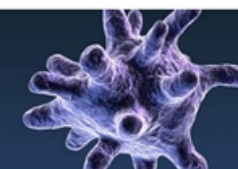
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PHASE 1

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PHASE 1

**CNS NLRP3**  
PRECLINICAL

**SUMMARY**  
MILESTONES & HIGHLIGHTS



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# VTX958 Program Summary

Allosteric, selective TYK2 inhibitor



## Potentially Differentiated TYK2 Inhibitor

- Selective, **allosteric** TYK2 inhibitor
- TYK2 functional selectivity can potentially differentiate clinical profile vs. less selective TYK2 inhibitors



## Clinically Validated Target

- Well established clinical efficacy in psoriasis, IBD and psoriatic arthritis with biologics targeting IL-12/IL-23 and IL-23\* pathways
- These pathways also the target of allosteric TYK2 inhibitors
- Phase 3 PoC in psoriasis has been demonstrated\*\* by BMS' allosteric TYK2 inhibitor deucravacitinib

*Deucravacitinib in Phase 2/3 for Crohn's disease, psoriatic arthritis, lupus*



## Large Addressable Markets

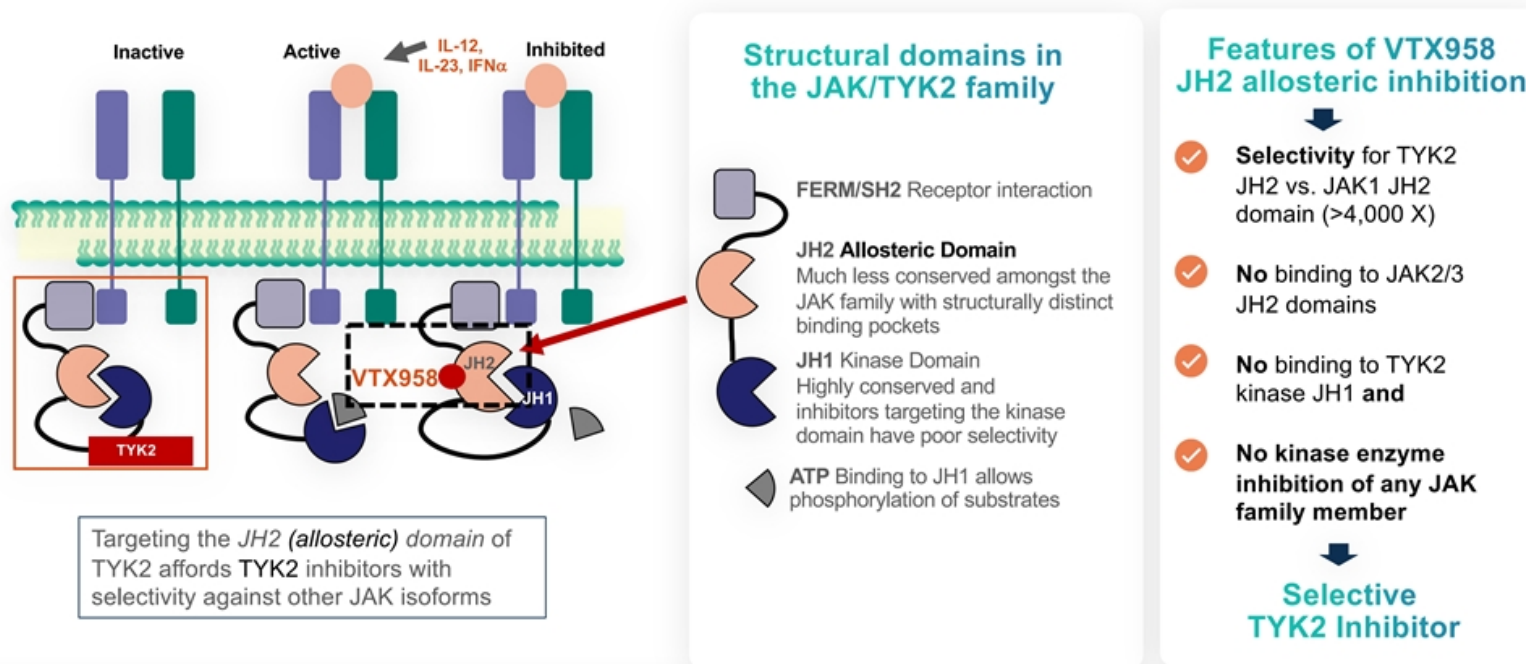
- Multiple autoimmune disorders in dermatology, IBD, renal and rheumatology total \$45B WW

Includes approved drugs Stelara™ (JNJ), Tremfya® (JNJ), Skyrizi™ (ABBV), Ilumya™ (Sun Pharma) and others in late-stage development (mirikizumab (LLY), brazikumab (AZN)

\*\*Deucravacitinib efficacy reported on 16-week primary endpoint of PASI-75 (75% reduction of psoriasis affected area and severity) at AAD '21; p<0.0001 vs placebo and Otezla® in POETKY-1; p=0.0003 vs. Otezla in POETKY-2; See slide 14 for more detail on \$45B worldwide market



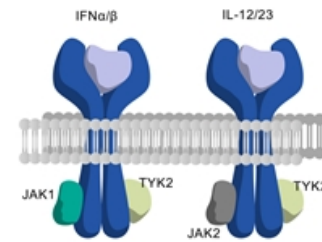
## Allosteric Inhibitor VTX958 Binds Selectively to the TYK2 JH2 Domain



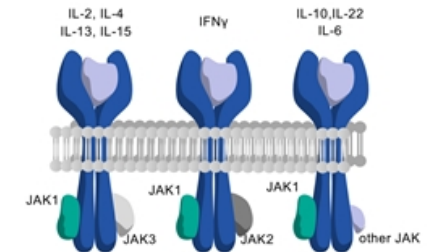
## VTX958 More Selective than Deucravacitinib for TYK2 JH2 Domain

Targeting JH2 domain selectively inhibits TYK2 pathways (IL-12, IL-23, IFN $\alpha$ ) while avoiding the JAK1/2/3 pathways

	DEUCRAVACITINIB	VTX958
TYK2-JH2 Binding $K_d$	0.009 nM	<b>0.058 nM</b>
JAK1-JH2 Binding $K_d$	0.43 nM	<b>240 nM</b>
Selectivity (fold)	48	<b>&gt;4,000</b>



TYK2 essential signaling pathways



JAK1 dependent signaling pathways

Source: Ventyx internal data

## VTX958 Selectively Targets IL-12, IL-23 and IFN $\alpha$

### VTX958 Potently Inhibits TYK2 Pathways

Selective and potent inhibition of IL-12/23 and Type I interferon axis allows targeting pathways driving immune-mediated diseases



### Proinflammatory Innate & Th1/Th17 Cytokines

#### Psoriasis Patient PBMC

Drug	IL-12 IC <sub>50</sub> (nM)	IL-23 IC <sub>50</sub> (nM)	IFN $\alpha$ IC <sub>50</sub> (nM)
VTX958	35	5	12
deucravacitinib	10	10	5

### VTX958 Has No Measurable Inhibition of JAK1-Mediated Pathways

Lack of inhibition of IL-6, IL-10 and other protective cytokines may avoid potential AEs associated with less selective inhibitors



### Pleiotropic Cytokines with Protective Functions

Drug	IL-22 IC <sub>50</sub> (nM)	IL-10 IC <sub>50</sub> (nM)	IFN $\gamma$ IC <sub>50</sub> (nM)	IL-4 IC <sub>50</sub> (nM)	IL-6 IC <sub>50</sub> (nM)
VTX958	>10,000	>10,000	>10,000	>10,000	>10,000
deucravacitinib	114	20	350	249	464

### Key Takeaways

Potent activity against IL-23, a key cytokine implicated in psoriasis and other indications

Broad therapeutic window with VTX958 may allow for higher exposures in Phase 2/Phase 3 studies

Source: Ventyx internal data; conducted in peripheral blood mononuclear cells (PBMC)

## VTX958 Phase 1 SAD Results Support Clinical Advancement



### SAFETY

Well-tolerated across all cohorts; all AEs observed were mild and not dose- or time-of-dose dependent



### PHARMACOKINETICS

No dose-saturation observed; PK and absorption profiles suggest continued absorption throughout GI tract

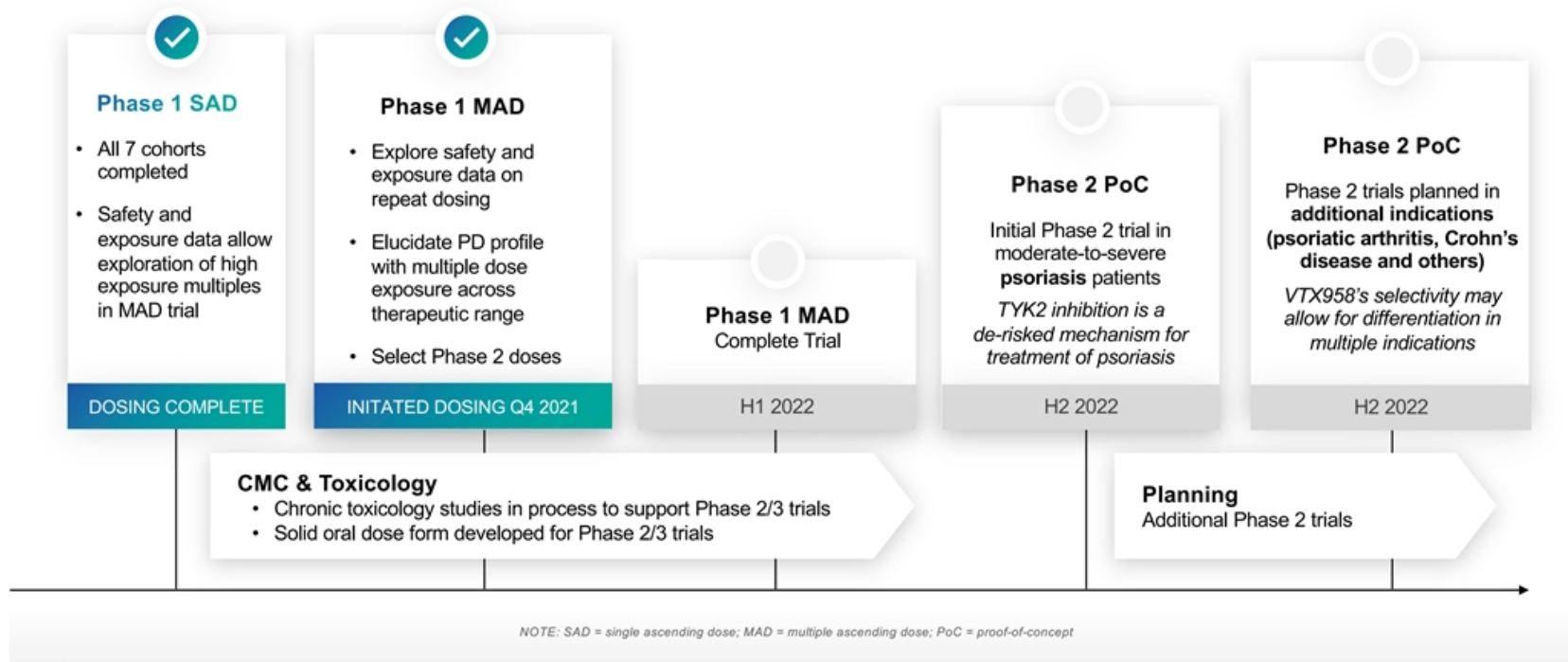


### PHARMACODYNAMICS

Dose-dependent VTX958-mediated effect on TYK2 signaling observed in both *in vivo* gene expression studies and *ex vivo* stimulation assays

NOTE: SAD = single ascending dose; AE= adverse event; dose-related exposures are observed at all doses

# VTX958 Clinical Development Plan



## Commercial Potential in Large Well-Established Markets

INDICATION*	PATIENTS IN THE U.S.	GLOBAL DRUG REVENUE* (2020)	TARGET POPULATION
<b>Psoriasis</b> <i>Dermatology</i>	<b>~8M</b>	<b>~\$20B</b>	<b>25-30%</b> MODERATE-TO-SEVERE
<b>Crohn's disease</b> <i>IBD</i>	<b>~700K</b>	<b>~\$13B</b>	<b>30-40%</b> MODERATE-TO-SEVERE
<b>Ulcerative colitis</b> <i>IBD</i>	<b>~1M</b>	<b>~\$7B</b>	<b>30-40%</b> MODERATE-TO-SEVERE
<b>Psoriatic arthritis</b> <i>Rheumatology</i>	<b>~1M</b>	<b>~\$4B</b>	<b>40-60%</b> MODERATE-TO-SEVERE
<b>SLE</b> <i>Rheumatology</i>	<b>Up to 500K</b>	<b>~\$1B</b>	

Sources: Evaluate Pharma, Company Estimates, Wall Street Research

\*Global drug revenue refers to the total market across all severity levels

Notes: SLE = systemic lupus erythematosus; \*Group of indications based on current mid/late-stage trials for BMS's allosteric TYK2 inhibitor deucravacitinib; global commercial sales totaled \$10.65B for biologics targeting IL-12/23 and IL-23 in 2020

# Psoriasis and Psoriatic Arthritis

## Commercial Snapshot

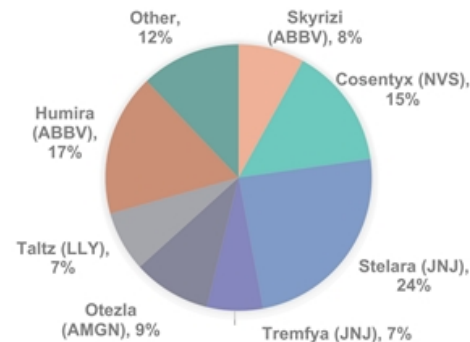
### Psoriasis Commercial Opportunity

- ~8M patients in U.S.
- 25-30% are moderate-to-severe
- U.S. biologic penetration ~15-20%
- Total treated U.S. moderate-severe population ~1.2m\*
- Global revenue of psoriasis drugs ~\$20B in 2020

**Leading Branded Drugs in the \$20B Worldwide Psoriasis Market**

### Psoriatic Arthritis Opportunity

- ~1M patients in U.S.
- Up to ~40-60% are moderate-to-severe
- Total treated U.S. moderate-severe population ~500k\*
- Global revenue of PsA drugs ~\$4B in 2020



### Key Takeaways

- Significant share shift in recent years from anti-TNF agents to newer biologics (anti-IL-23, IL-12/23 and anti-IL-17s antibodies)
- Despite limitations, Otezla had \$2.2B in 2020 sales and is the only major oral player in these markets
- TYK2 de-risked in both indications by deucravacitinib
  - Psoriasis: Phase 3 trial 6mg QD dose was statistically superior vs. Otezla\*
  - PsA Phase 2 data showed stat. significant ACR20 and ACR50 scores vs pbo^; now in Phase 3 trials at 6mg QD dosing

Sources: Evaluate Pharma, Company Estimates, Wall Street Research; \*BMS AAD 2021 Presentation; PsA=psoriatic arthritis; \*BMS deucravacitinib: 54-59% responses on PASI75 at 16 weeks achieved statistically significant results vs. apremilast control  
 ^6/12mg ACR20: 53/63% vs 32%; ACR50: 24/33% vs 11%

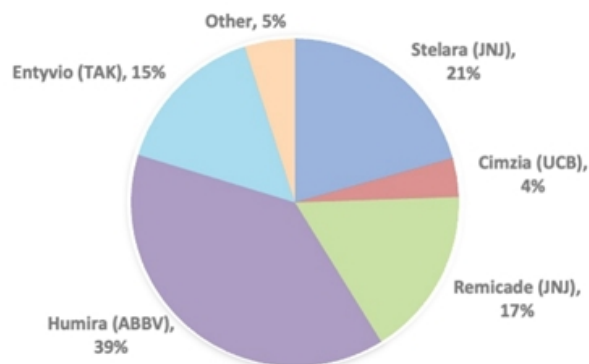
# Crohn's Disease

## Commercial Snapshot

### Crohn's Disease (IBD) Commercial Opportunity

- ~700k+ Crohn's disease patients in U.S.
- 30-40+% are moderate-to-severe
- U.S. biologic penetration ~35-40%
- Global revenue of Crohn's disease drugs ~\$13B in 2020

### 2020 Market Share of Leading Branded Drugs in the \$13B WW Crohn's Disease Market

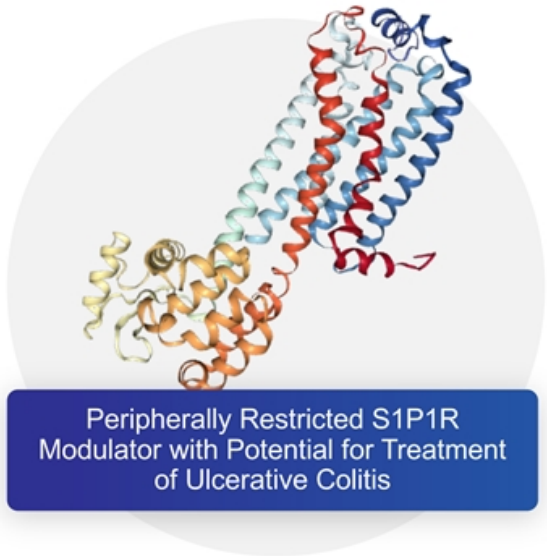


Sources: Evaluate Pharma, Company estimates, Wall Street research, BMS AAD 2021 Presentation; Skyrizi label dosing for psoriasis/PsA vs. Phase 3 Crohn's dosing regimen

### Key Takeaways

- ~\$13B market dominated by parenteral biologic therapies
- Share trends have favored Stelara (anti-IL-12/23) with more selective anti-IL-23 biologics (i.e. Skyrizi) producing positive Phase 3 data
- Dosing of IL-23 targeting biologics in CD may be as great as 3-4x dosing in dermatology indications
- Biologics targeting anti-IL12/23 and anti-IL23 provide rationale for TYK2 inhibitor development; higher selectivity may yield wider therapeutic index, potentially supporting differentiation





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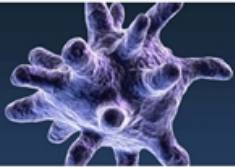
**VTX958**  
PHASE 1

**VTX002**  
PHASE 2 READY

**VTX2735**  
PHASE 1

**CNS NLRP3**  
PRECLINICAL

**SUMMARY**  
MILESTONES & HIGHLIGHTS



**ventyx**  
BIOSCIENCES

# VTX002 Program Summary

Phase 2 ready S1P1R modulator for ulcerative colitis



## Potentially Differentiated S1P1R Modulator

- Selective S1P1R modulator
- Differentiated on key parameters
- Demonstrated pharmacodynamic activity in Phase 1 trial
- Pursuing clinical development plan in both treatment-naïve and biologic-experienced patients



## Clinically-Validated Target

- S1P1R modulators approved for MS and UC with clinical trials ongoing in other indications
- BMS' ozanimod approved for UC in May 2021



## Large Addressable Market

- Ulcerative colitis is lead indication totaling up to \$7B in worldwide revenue

## VTX002 Differentiates on Multiple Key Parameters vs. Competitors



### Potential for Differentiated Clinical Profile in UC Patients

Sustained lymphocyte reduction up to 65% across multiple doses in MAD trial



### Safety Profile

No SAEs, elevated LFTs, abnormal PFTs or macular edema



### No Drug-Drug Interactions

No CYP inhibition; no food effect; favorable profile for patients with co-morbidities



### Fast Onset of Action Faster Lymphocyte Recovery

No long-acting circulating metabolites  
Optimal half life (t~20h)



### Ability to Dose Titrate

Potential to avoid first-dose cardiac monitoring in label



### Peripherally Restricted

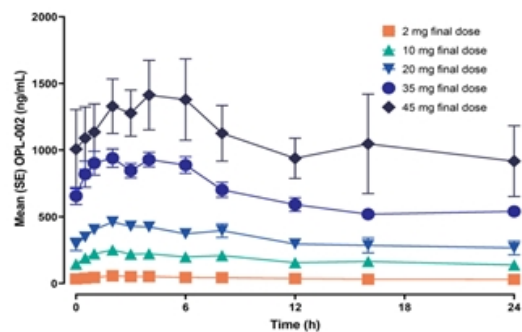
Very low CNS penetration; not a repurposed MS drug; potential to avoid macular edema

Notes: SAE=significant adverse event; MAD=multiple ascending dose

## Phase 1 MAD Results: Dose-Dependent Exposure and Lymphocyte Reduction

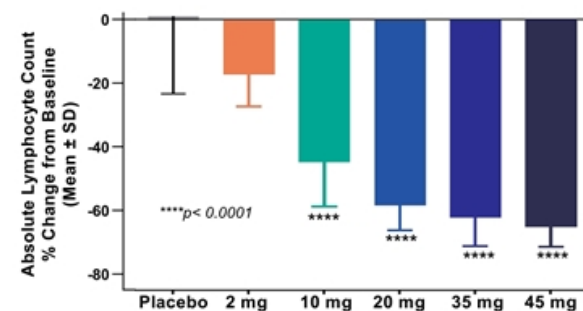
Absolute lymphocyte count (ALC) reductions of 40-50% correlated with clinical efficacy observed in UC\*

### Pharmacokinetics



- $T_{1/2}$  of ~20 hours
- Dose-proportionate exposure after single and multiple doses of VTX002 with steady-state reached after 4 to 7 days of target-dose exposure

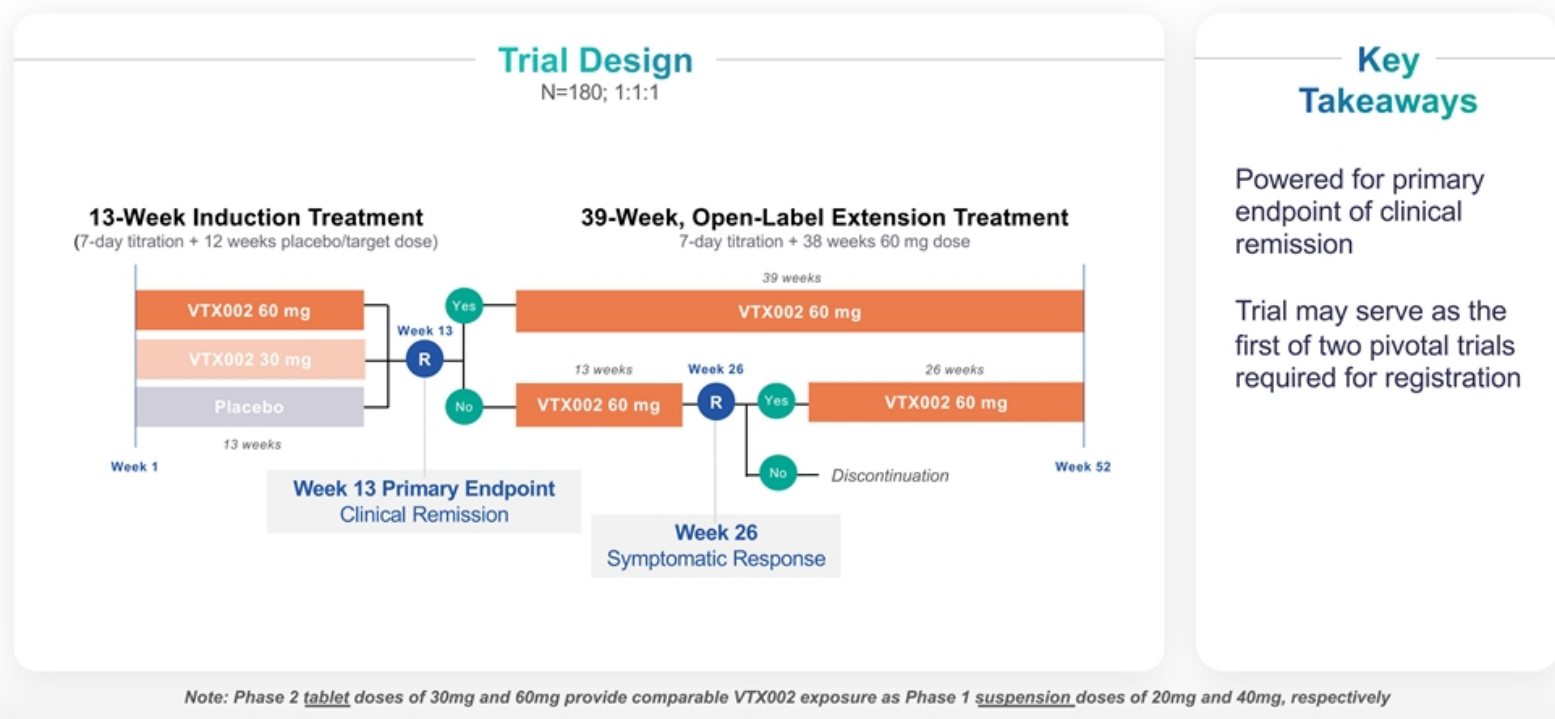
### Pharmacodynamics



- Demonstrated consistent, sustained reduction of lymphocytes up to 65% across multiple dose groups

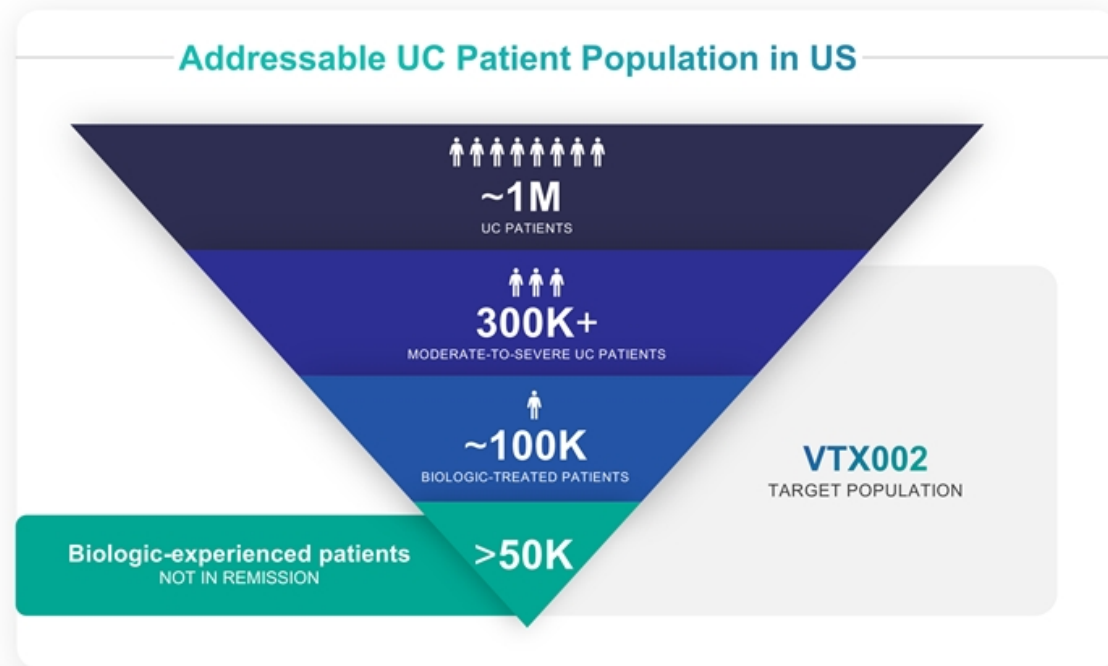
Source: NEJM (2016), Gastroenterology (2020)  
\*Ph2 UC ALC reduction from baseline: 1mg ozanimod (49%), 2mg etrasimod (40%)

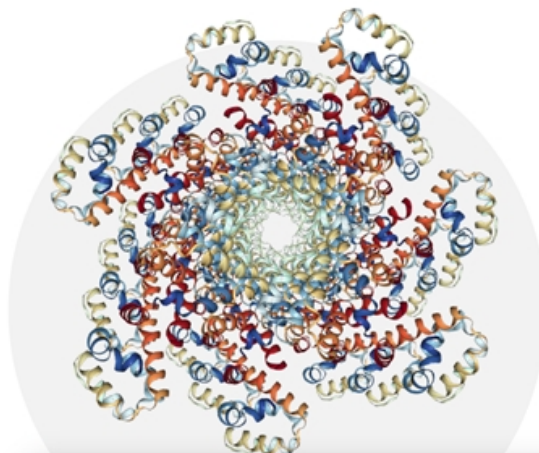
## Phase 2 Trial in Moderate-to-Severe Ulcerative Colitis Patients



## Underpenetrated Market for Biologic Refractory Patients

- Existing agents leave room for new treatments
- Novel oral agents may expand penetrance of treated moderate-to-severe UC population beyond current ~25-30%
- S1P well positioned to emerge as leading oral therapeutic class based on its attractive class efficacy/safety profile





Selective NLRP3 Inflammasome  
Inhibitors for Systemic  
and CNS Indications

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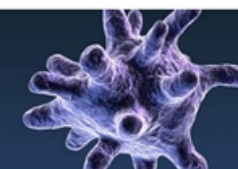
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# Rationale for Targeting the NLRP3 Inflammasome

NLRP3 inflammasome inhibitors target IL-1 $\beta$ , a key driver of inflammatory disease



## In vivo evidence

- The NLRP3 inflammasome can become overactive in the presence of persistent tissue damage or crystal deposits
- Inflammasome activation results in release of IL-1 $\beta$  & IL-18 recruiting neutrophils and driving Th17 response
- This leads to pyroptosis and further tissue damage



## Genetic evidence

- Gain-of-function mutations in the NLRP3 gene, associated with certain severe orphan inflammatory diseases, are classified as cryopyrin-associated periodic syndromes (CAPS)



## Clinical validation of downstream target

- IL-1 $\beta$  signaling, downstream of inflammasome activation, is a clinically-validated, anti-inflammatory target with biologics
- Ilaris® (\$873M sales in 2020) approved for CAPS and other orphan periodic fever syndromes

NLRP3 = NOD-like receptor family, pyrin domain-containing protein 3; IL-1 $\beta$  = interleukin-1 $\beta$



## NLRP3 Inhibitor Program Summary



### Peripheral NLRP3 Inhibitor: VTX2735

- Selective NLRP3 inhibitor
- Well tolerated in GLP safety and tox assessment
- Phase 1 dosing initiated in Q4 2021
- High oral bioavailability in non-clinical PK studies
- PD activity demonstrated in animal models

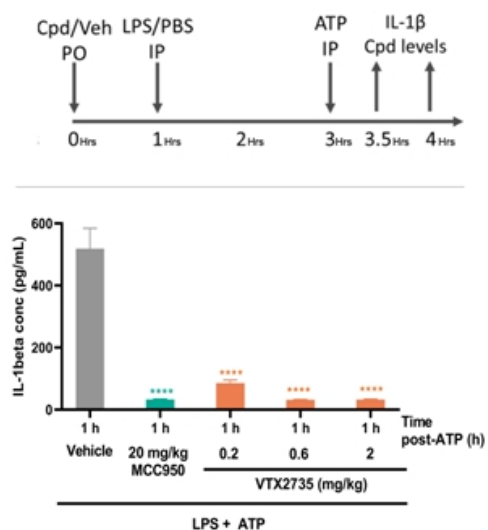


### CNS NLRP3 Inhibitor

- Currently in late-stage lead optimization
- Selective compounds generated with high CNS bioavailability
- Novel and proprietary lead series
- Potential to be first, truly CNS-directed NLRP3 inhibitor in clinic

# VTX2735 is a Selective & Orally Bioavailable NLRP3 Inhibitor

## Mouse Pharmacodynamic Assay

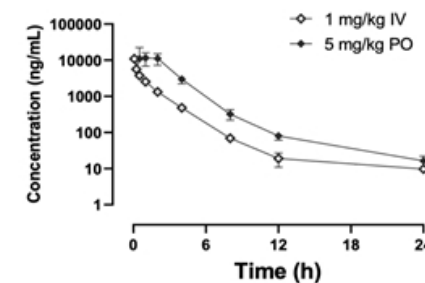


## In Vitro Potency & Selectivity

	IL-1β IC <sub>50</sub> (nM)	VTX2735
On Target	human monocytes	2
	human whole blood	48
Off Target	AIM2	>10000
	NLRC4	>10000
	NF-kb	>10000

## Non-Human Primate PK

IV Clearance: 1.6 mL/min/kg; Oral Bioavailability: 80%



## Key Takeaways

- Well-tolerated preclinically in IND-enabling GLP studies
- Oral bioavailability (80%) in NHP and dose-proportional exposure that predicts potential for wide safety margins based on PK/PD modeling

MCC950 is an NLRP3 inhibitor and a control compound used in in vitro and in vivo studies

# VTX2735 Has Broad Activity Against Multiple NLRP3 Mutations

## Potential for Differentiation in CAPS Setting\*

### What is CAPS?

An ultra-orphan auto-inflammatory disease caused by various mutations in NLRP3 and characterized by inappropriate release of IL-1 $\beta$  and symptoms of recurrent systemic inflammation

### Key Takeaway

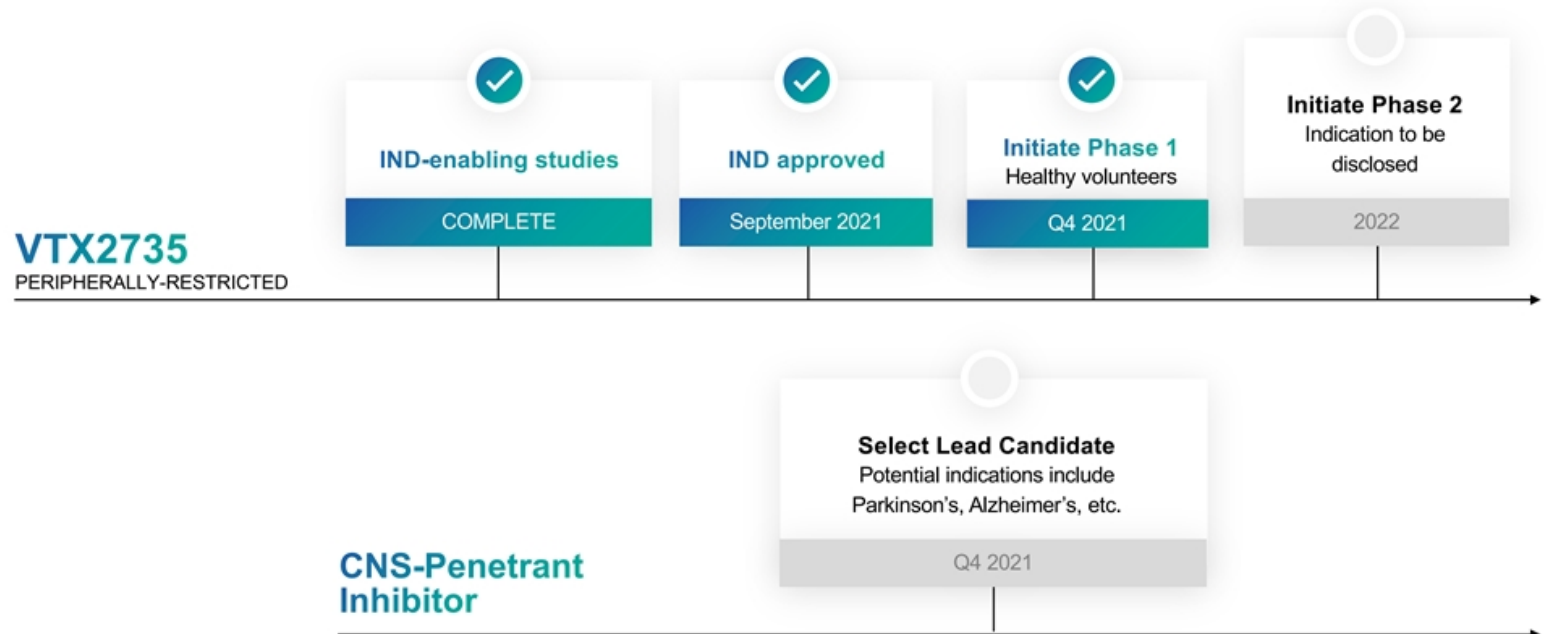
VTX2735 blood assay data from CAPS patients suggest inhibitory activity across several mutations: FCAS, MWS and NOMID subset of CAPS patients

### IC<sub>50</sub> in blood monocyte assay (nM)

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

\*Source: UCSD (Dr. Hal Hoffman's lab); CAPS=Cryopyrin-Associated Periodic Syndromes

## NLRP3 Program Clinical Development Plan



# Our Comprehensive NLRP3 Portfolio Targets a Broad Range of Major Inflammatory Diseases

## Neuroinflammatory Diseases

CNS-directed NLRP3 inhibitors are designed to treat a range of neurodegenerative disorders, such as Alzheimer's and Parkinson's disease



*Alzheimers' Disease*  
*Parkinson's Disease*  
*ALS*

**NLRP3**

## Systemic Diseases

Peripheral NLRP3 inhibitors are designed to treat cardiovascular, rheumatic, fibrotic and rare genetic diseases



*Cardiovascular*  
*Rheumatic*  
*Fibrotic Diseases*  
*Rare Genetic Diseases*

## Tissue-Specific Diseases

Tissue-specific NLRP3 inhibitors are designed to treat conditions associated with site-specific inflammation, such as IBD, pulmonary and dermatologic diseases



*Fibrotic Lung Disease*  
*Liver Disease*  
*Skin Diseases*



**COMPANY**  
TEAM, INVESTORS, & PIPELINE

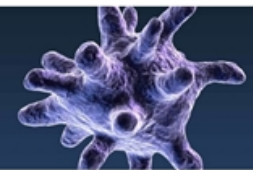
**VTX958**  
PHASE 1

**VTX002**  
PHASE 2 READY





**VTX2735**  
PHASE 1

**CNS NLRP3**  
PRECLINICAL

**SUMMARY**



## Projected Catalysts Over Next 24 Months

PROGRAMS	H2'2021	H1'2022	H2'2022	2023
 <p>Allosteric TYK2 inhibitor addressing a broad range of autoimmune disorders</p>	Phase 1 SAD	Phase 1 MAD	Phase 2 in Multiple Indications*	
 <p><b>VTX002</b> Selective S1P1R modulator targeting UC and other immune disorders</p>		Phase 2 Ulcerative Colitis 13-Week Induction		
 <p><b>VTX2735</b> Peripheral NLRP3 inflammasome inhibitor for multiple inflammatory and immune conditions</p>	IND-enabling	Phase 1 SAD/MAD	Phase 2 PoC Initiation	
 <p><b>VTX CNS</b> CNS-directed NLRP3 inflammasome inhibitor for neurodegenerative diseases</p>	Candidate Selection	IND-enabling	Phase 1 SAD/MAD**	

\*Following completion of our Phase 1 trial, we intend to initiate Phase 2 PoC trials in psoriasis, psoriatic arthritis, Crohn's disease and potentially other indications

\*\* Following regulatory acceptance of planned H2 2022 IND filing, we intend to initiate and conduct a Phase 1 SAD/MAD trial in healthy volunteers

## Investment Highlights

### Efficient & Productive Immunology Platform

**Internal R&D engine** designed to generate candidates to address autoimmune and inflammatory diseases with high unmet need

**100% commercial rights** to entire portfolio; long patent life for all product candidates

### Potentially Differentiated Medicines

**Multiple selective, oral, small molecule product candidate portfolio:**

- **VTX958:** *allosteric TYK2 inhibitor for multiple autoimmune indications*
- **VTX002:** *peripherally-restricted S1P1R modulator for ulcerative colitis*
- **VTX2735:** *a peripheral NLRP3 inhibitor for multiple autoimmune indications, and CNS-targeted NLRP3 inhibitors*

### Target Major Inflammatory & Immunology Disease Markets

**Our portfolio can address I&I markets**, such as psoriasis, IBD, and other indications

Opportunity to disrupt existing markets dominated by biologics with varying degrees of efficacy and safety in order to:

- ✓ *Capture refractory patients*
- ✓ *Expand market share of moderate-to-severe patient populations with patient-friendly oral therapy*

### Capital-Efficient Business Model

**Over \$339 million raised** from dedicated biotech investors

**Cash balance of \$142M** as of September 30, 2021\*

\*Not including gross proceeds of \$174M raised in October 2021 IPO





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