



Corporate Presentation

First Quarter 2022

Forward Looking Statements

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COMPANY

INTRODUCTION AND PIPELINE

VTX958

TYK2 INHIBITOR,
PHASE 1

VTX002

S1P1R MODULATOR,
PHASE 2

VTX2735

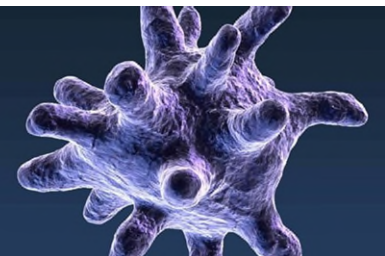
PERIPHERAL NLRP3 INHIBITOR,
PHASE 1

CNS NLRP3 Inhibitor

PRECLINICAL

SUMMARY

MILESTONES & HIGHLIGHTS



Our Leadership Team

Management



Martin Auster, MD
CHIEF FINANCIAL OFFICER



John Nuss, PhD
CHIEF SCIENTIFIC OFFICER



Raju Mohan, PhD
CHIEF EXECUTIVE OFFICER, FOUNDER



Chris Krueger, JD
CHIEF BUSINESS OFFICER



Jörn Drappa, MD, PhD
CHIEF MEDICAL OFFICER

Board of Directors

Sheila Gujrathi, MD
EXECUTIVE CHAIR, VENTYX

Jigar Choksey
PRINCIPAL, THIRD POINT

Richard Gaster, MD, PhD
MANAGING PARTNER, VENBIO

Raju Mohan, PhD
CHIEF EXECUTIVE OFFICER,
VENTYX

Aaron Royston, MD
MANAGING PARTNER,
VENBIO

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



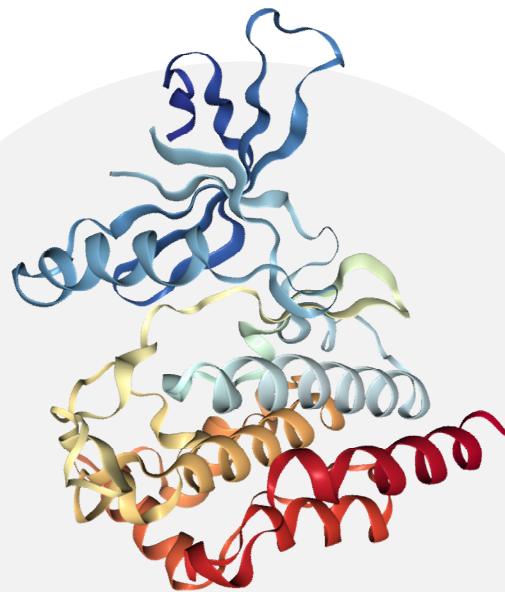
Our experienced team and our internal R&D engine
continue to generate candidates with potential to address diseases with high unmet need

Broad Pipeline of Candidates With Multiple Near-Term Catalysts

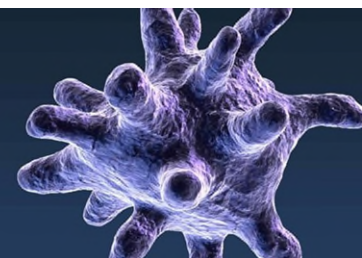
Addressing Established Inflammatory and Immunology Markets with Wholly Owned Product Portfolio

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





Orally Bioavailable,
Selective Allosteric
Inhibitor of TYK2



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



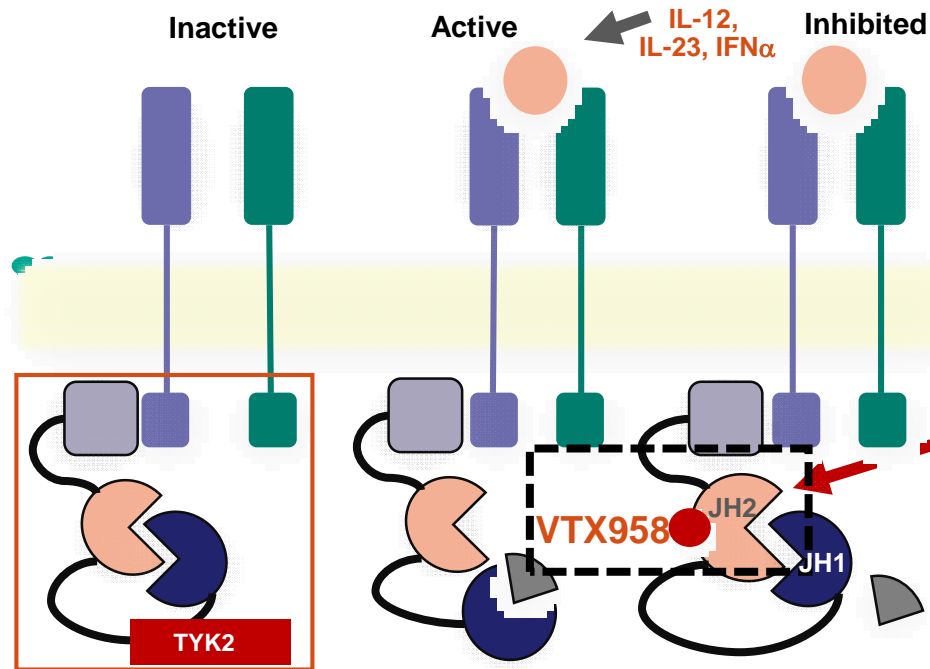
Large Addressable Markets

- 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))

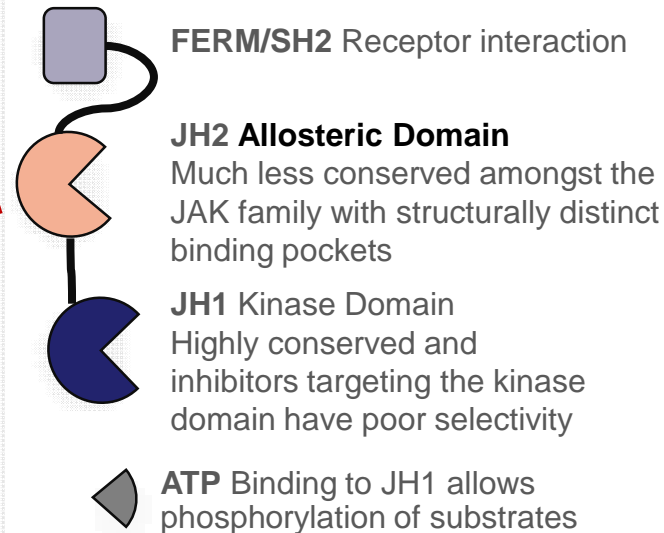
***Deucravacitinib efficacy reported on 16-week primary endpoint of PASI-75 (75% reduction of psoriasis affected area and severity) at AAD '21; p<0.0001 vs placebo and Otezla® in POETKY-1; p=0.0003 vs. Otezla in POETKY-2; See slide 14 for more detail on \$45B worldwide market*

Allosteric Inhibitor VTX958 Binds Selectively to the TYK2 JH2 Domain



Targeting the *JH2* (allosteric) domain of TYK2 affords TYK2 inhibitors with selectivity against other JAK isoforms

Structural domains in the JAK/TYK2 family



Features of VTX958 JH2 allosteric inhibition

- ✓ **Selectivity** for TYK2 JH2 vs. JAK1 JH2 domain (>4,000 X)
- ✓ **No** binding to JAK2/3 JH2 domains
- ✓ **No** binding to TYK2 kinase JH1 and
- ✓ **No** kinase enzyme inhibition of any JAK family member

Selective TYK2 Inhibitor

VTX958 More Selective than Deucravacitinib for TYK2 JH2 Domain

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

	DEUCRAVACITINIB	VTX958
TYK2-JH2 Binding K_d	0.009 nM	0.058 nM
JAK1-JH2 Binding K_d	0.43 nM	240 nM
Selectivity (fold)	48	>4,000

IFN α / β IL-12/23

JAK1 TYK2 JAK2 TYK2

TYK2 essential signaling pathways

IL-2, IL-4, IL-13, IL-15 IFN γ IL-10, IL-22, IL-6

JAK1 JAK3 JAK1 JAK2 JAK1 other JAK

JAK1 dependent signaling pathways

Source: Ventyx internal data

VTX958 Selectively Targets IL-12, IL-23 and IFN α

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	Psoriasis Patient PBMC		
	IL-12 IC ₅₀ (nM)	IL-23 IC ₅₀ (nM)	IFN α IC ₅₀ (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 ₅₀ (nM)	IL-10 IC ₅₀ (nM)	IFN γ IC ₅₀ (nM)	IL-4 IC ₅₀ (nM)	IL-6 IC ₅₀ (nM)
	IC ₅₀ (nM)	IC ₅₀ (nM)	IC ₅₀ (nM)	IC ₅₀ (nM)	IC ₅₀ (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

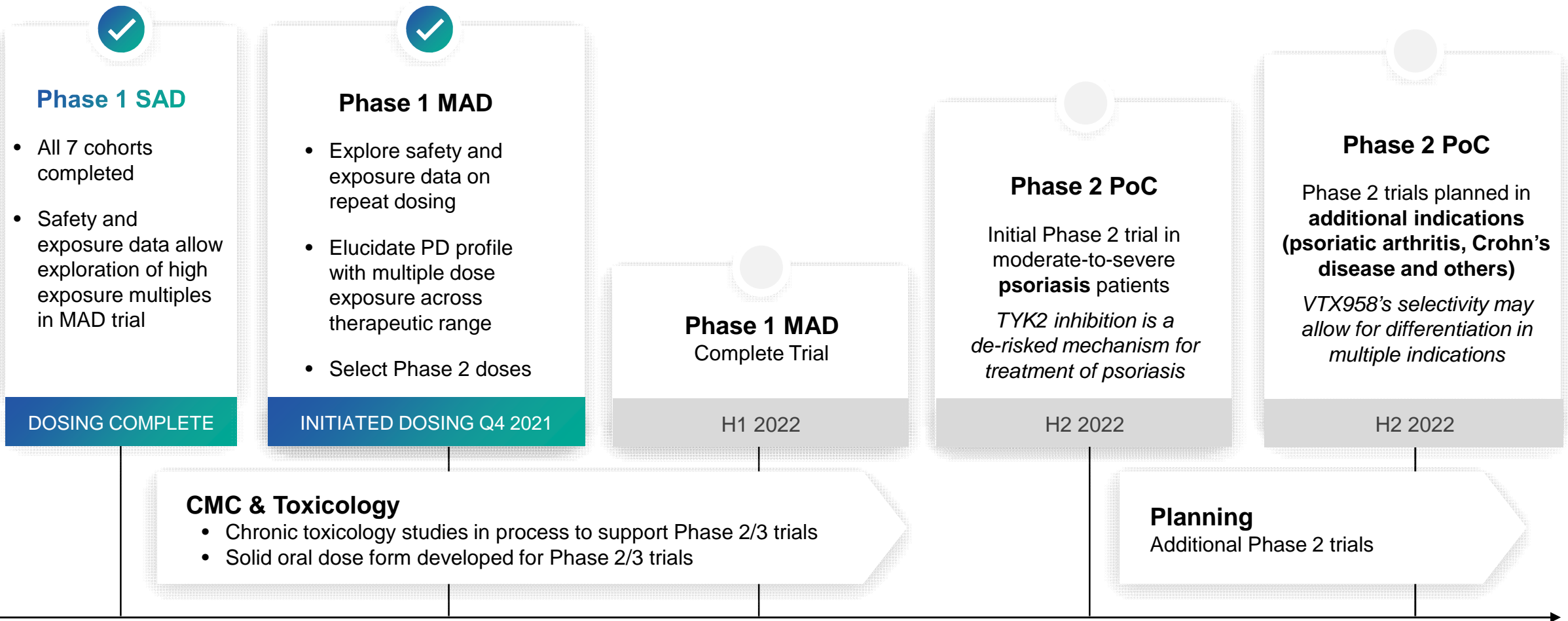


PHARMACODYNAMICS

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



NOTE: SAD = single ascending dose; MAD = multiple ascending dose; PoC = proof-of-concept

Commercial Potential in Large Well-Established Markets

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

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

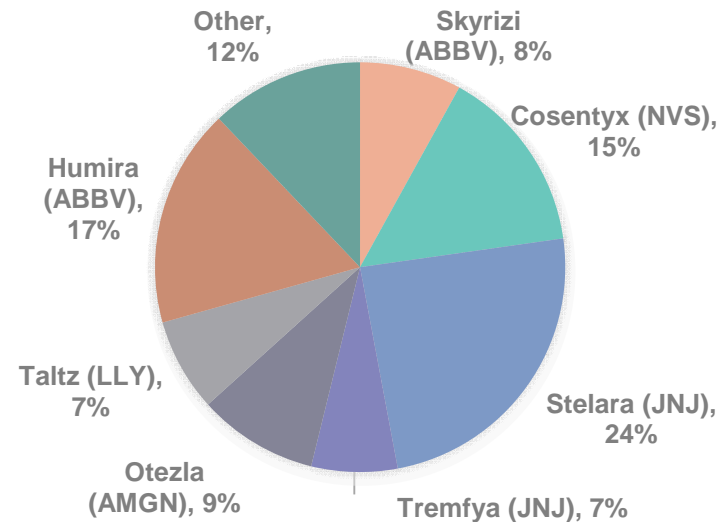
Psoriasis Commercial Opportunity

- ~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**

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**

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



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%

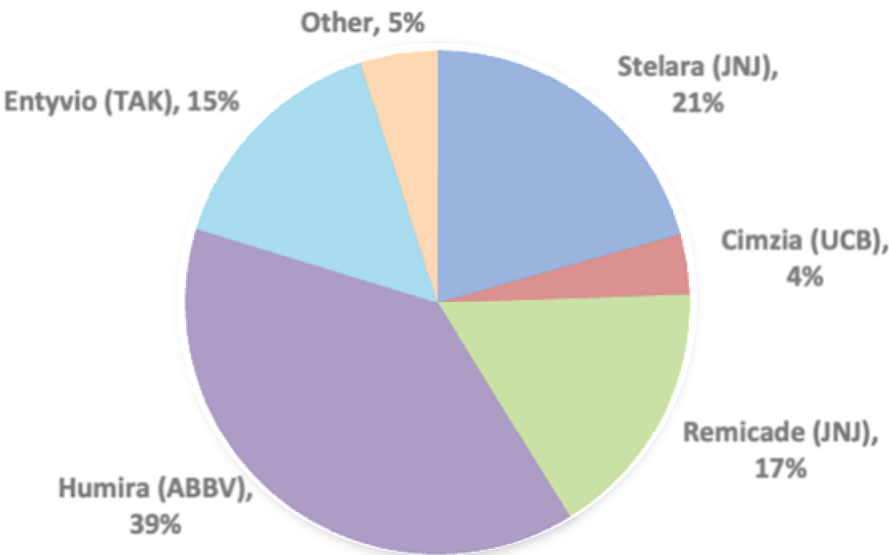
Crohn's Disease

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

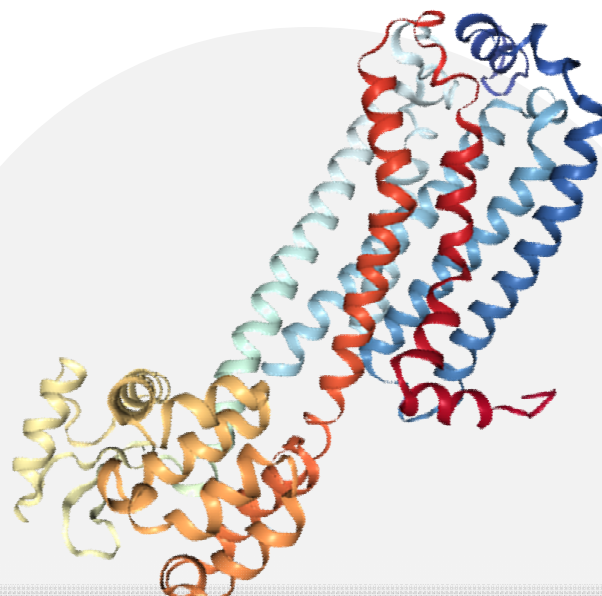
2020 Market Share of Leading Branded Drugs in the \$13B WW Crohn's Disease Market



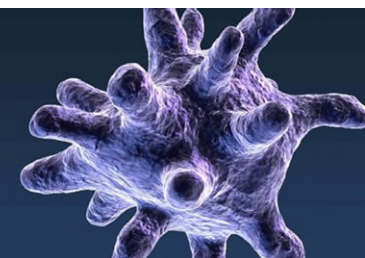
Key Takeaways

- ~\$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

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



Peripherally Restricted S1P1R
Modulator with Potential for Treatment
of Ulcerative Colitis



VTX002 Program Summary

Phase 2 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

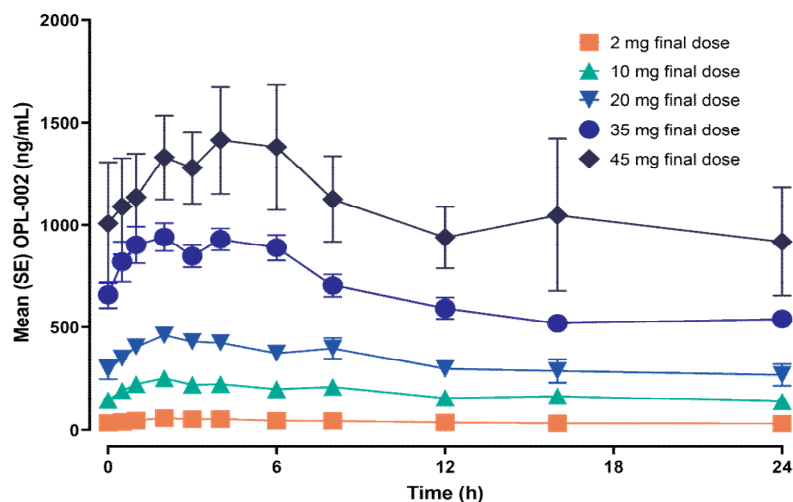
Very low CNS penetration; not a repurposed MS drug; potential to avoid macular edema

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

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

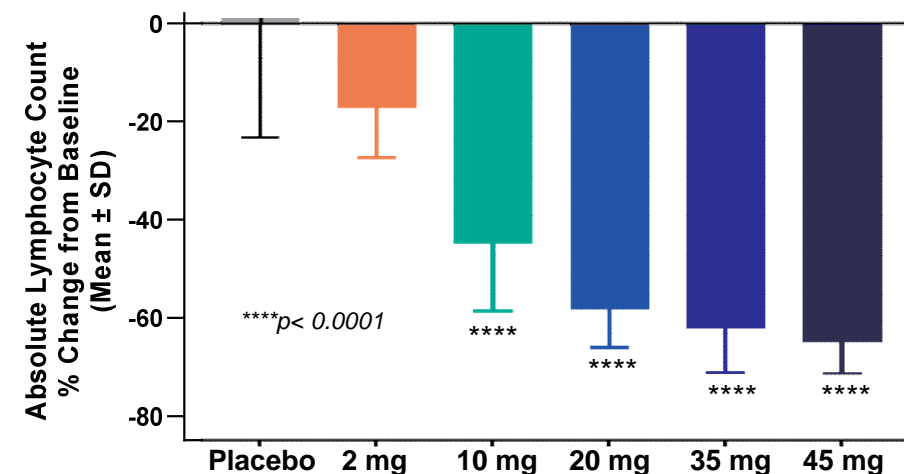
Absolute lymphocyte count (ALC) reductions of 40-50% correlated with clinical efficacy observed in UC*

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%)

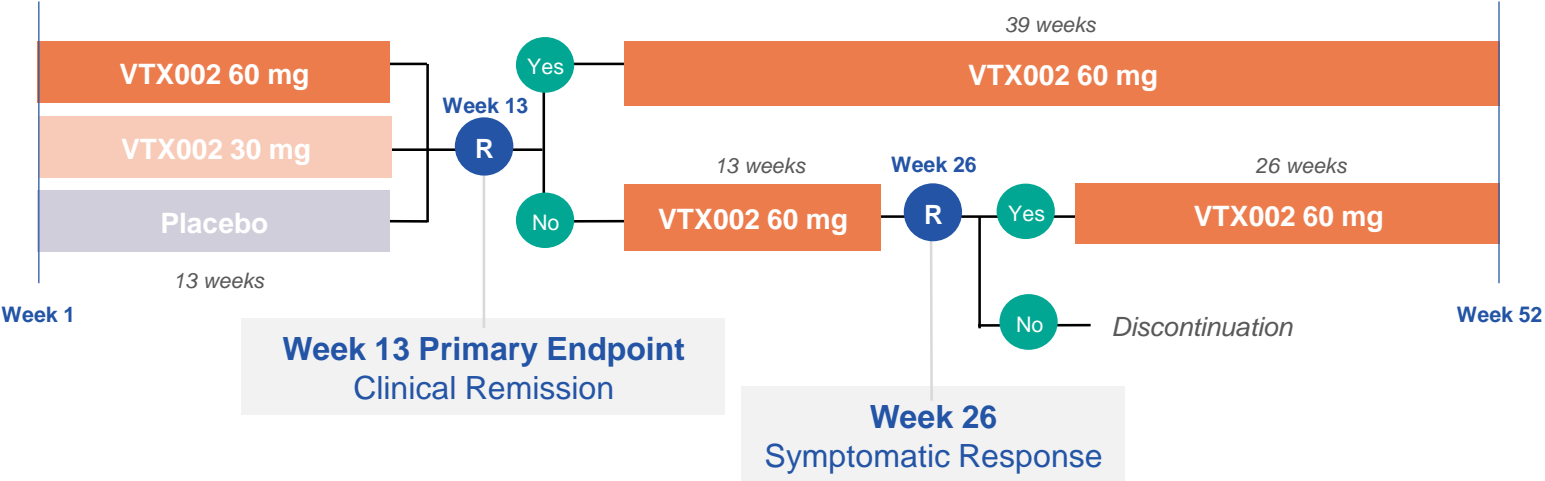
Phase 2 Trial in Moderate-to-Severe Ulcerative Colitis Patients

Trial Design

N=180; 1:1:1

13-Week Induction Treatment

(7-day titration + 12 weeks placebo/target dose)



Key Takeaways

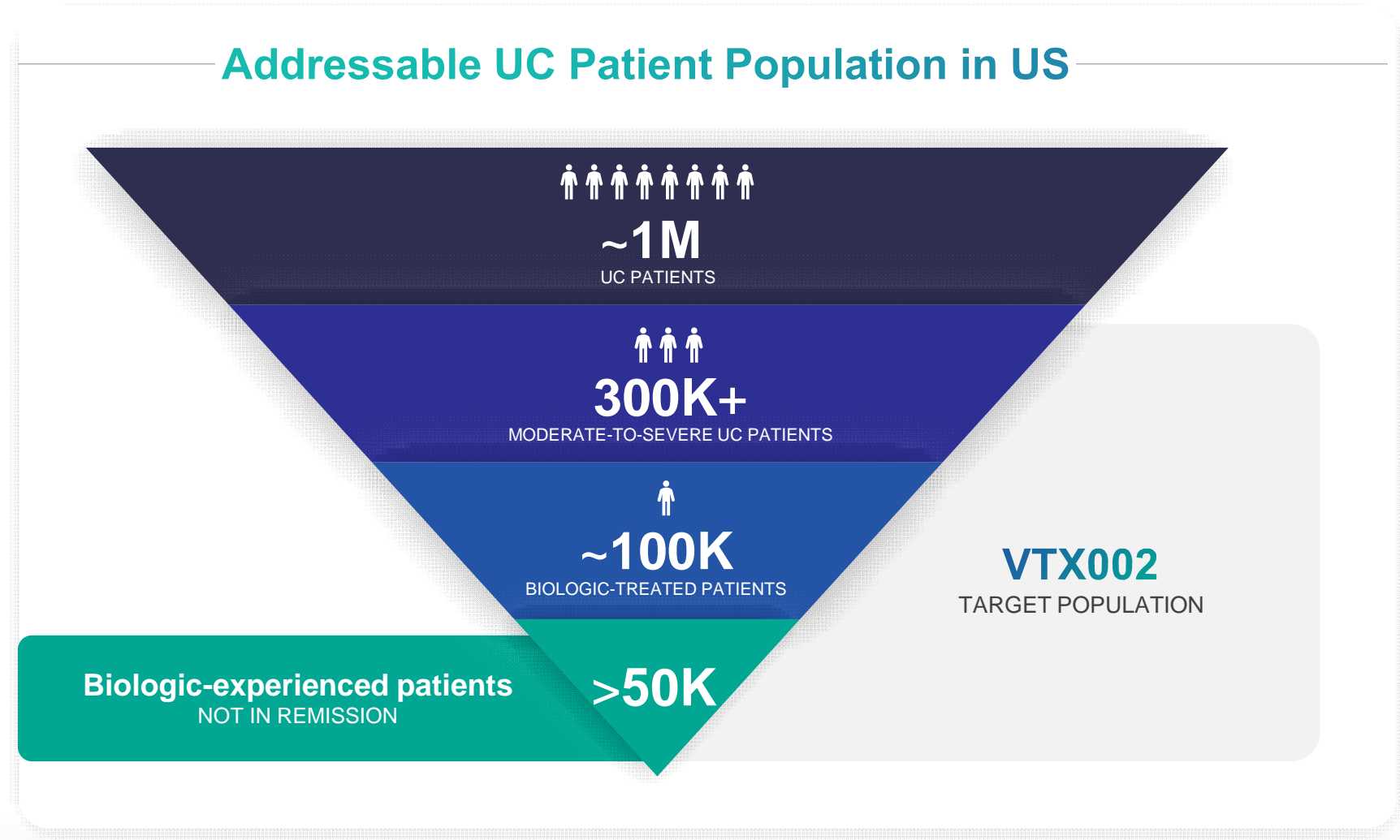
Powered for primary endpoint of clinical remission

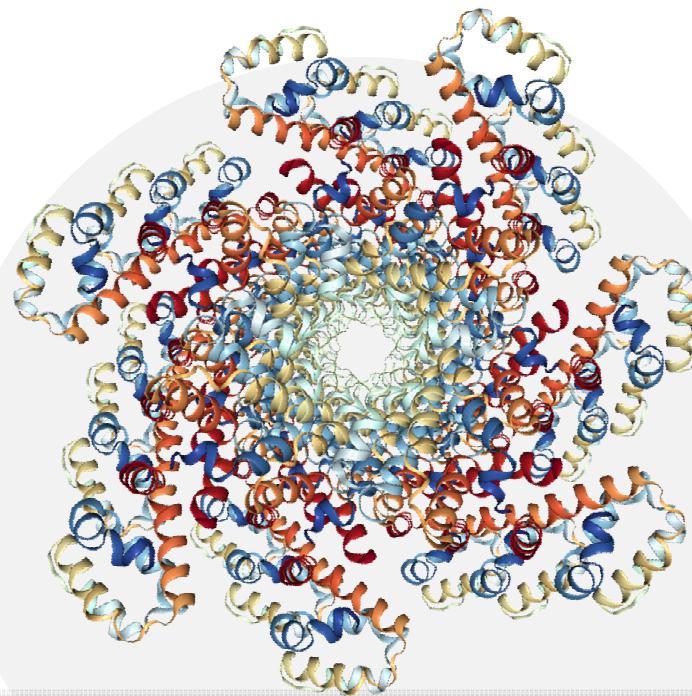
Trial may serve as the first of two pivotal trials required for registration

Note: Phase 2 tablet doses of 30mg and 60mg provide comparable VTX002 exposure as Phase 1 suspension doses of 20mg and 40mg, respectively

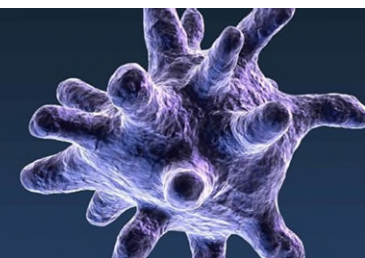
Underpenetrated Market for Biologic Refractory Patients

- 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



Rationale for Targeting the NLRP3 Inflammasome

NLRP3 inflammasome inhibitors target IL-1 β , 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 β & 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 β 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 β = interleukin-1 β

NLRP3 Inhibitor Program Summary



Peripheral NLRP3 Inhibitor: VTX2735

- Selective NLRP3 inhibitor
- Well tolerated in GLP safety and tox assessment
- Phase 1 ongoing, expected to complete dosing in H1 2022
- High oral bioavailability in non-clinical PK studies
- PD activity demonstrated in animal models



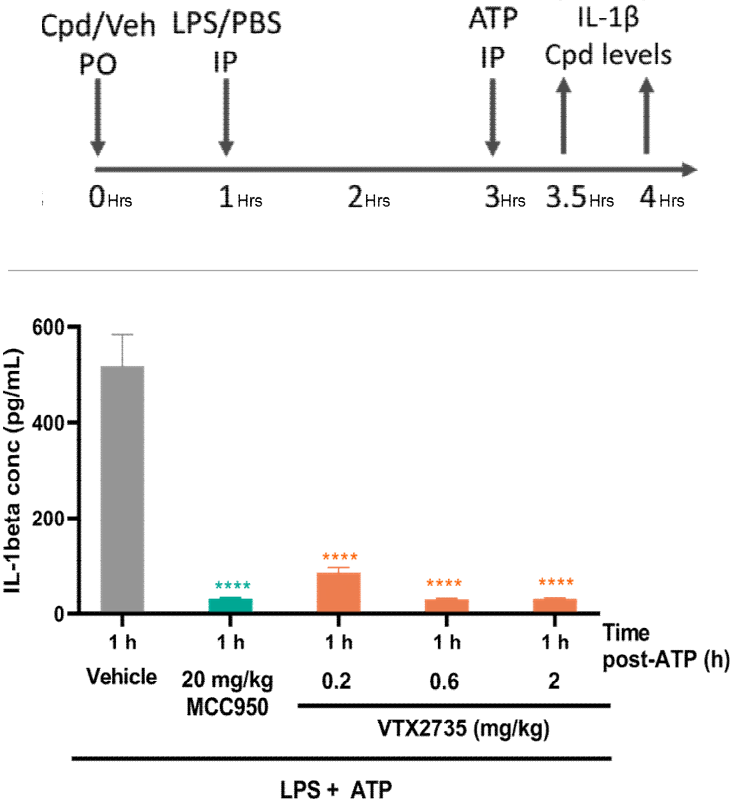
CNS NLRP3 Inhibitor

- Selective compounds generated with high CNS bioavailability
- Novel and proprietary lead series
- Plan to enter IND enabling studies 2022
- Potential to be first, truly CNS-directed NLRP3 inhibitor in clinic



VTX2735 is a Selective & Orally Bioavailable NLRP3 Inhibitor

Mouse Pharmacodynamic Assay

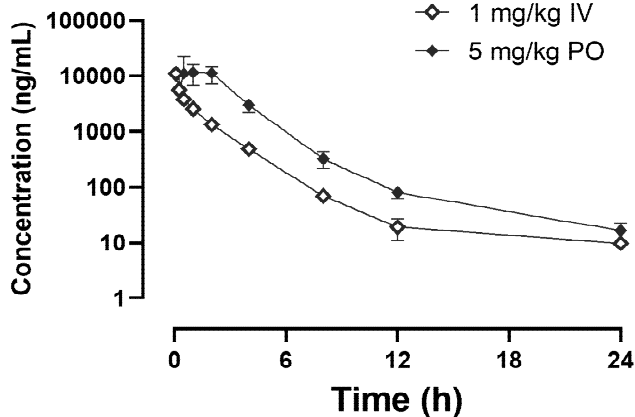


In Vitro Potency & Selectivity

	IL-1 β IC ₅₀ (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 β 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

IC₅₀ in blood monocyte assay (nM)

75%
of all CAPS patients
In North America

**MOST
SEVERE**

CPD	CHALLENGE	FCAS1 L353P	FCAS2 (L353P)	FCAS3 (L353P)	FCAS4 A439V/G564R	FCAS.MWS E525K/V198M	NOMID F309Y
VTX2735	LPS	117	56	166	14	24	17
MCC950	LPS	>10K	>10K	>10K	1,264	>10K	>10K

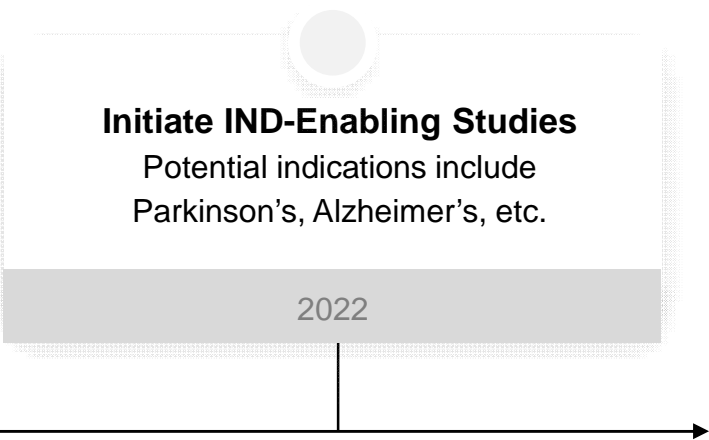
*Source: UCSD (Dr. Hal Hoffman's lab); CAPS=Cryopyrin-Associated Periodic Syndromes

NLRP3 Program Clinical Development Plan

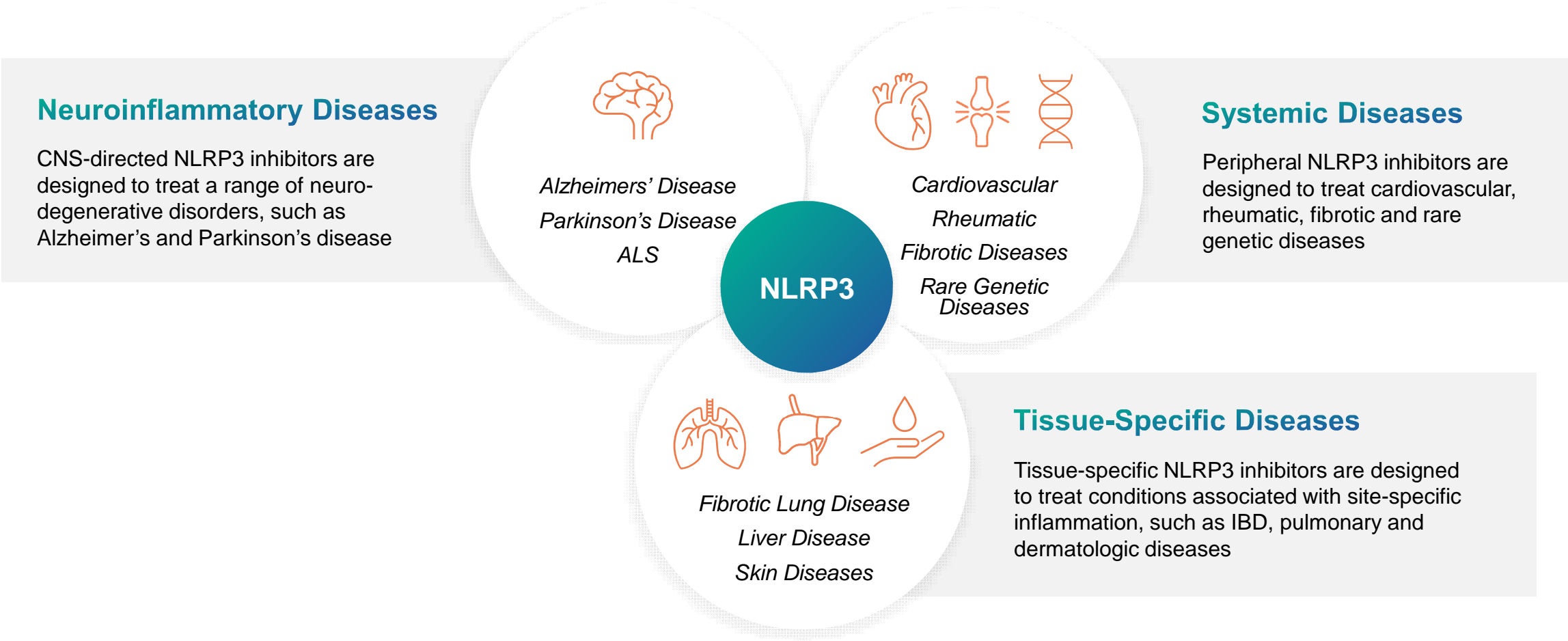
VTX2735
PERIPHERALLY-RESTRICTED



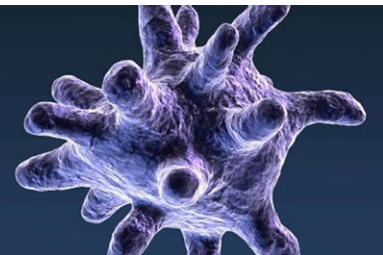
CNS-Penetrant Inhibitor



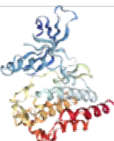
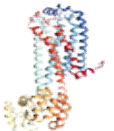
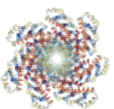
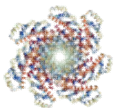
Our Comprehensive NLRP3 Portfolio Targets a Broad Range of Major Inflammatory Diseases



Projected Pipeline Catalysts and Summary



Projected Catalysts Over Next 24 Months

PROGRAMS			H2'2021	H1'2022	H2'2022	2023
	VTX958 Allosteric TYK2 inhibitor addressing a broad range of autoimmune disorders		Phase 1 SAD	Phase 1 MAD	Phase 2 in Multiple Indications*	
	VTX002 Selective S1P1R modulator targeting UC and other immune disorders		Phase 2 Ulcerative Colitis 13-Week Induction			
	VTX2735 Peripheral NLRP3 inflammasome inhibitor for multiple inflammatory and immune conditions		IND-enabling	Phase 1 SAD/MAD	Phase 2 PoC Initiation	
	VTX CNS CNS-directed NLRP3 inflammasome inhibitor for neurodegenerative diseases		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



Ventyx Biosciences, Inc.
662 Encinitas Boulevard, Suite 250
Encinitas, CA 92024

Contact us for additional information:
ir@ventyxbio.com