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# Virtual Investor Event

**March 11, 2024**

# Forward Looking Statements

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# Ventyx Virtual Investor Event

## Speakers and Participants

### Ventyx Team

- **Raju Mohan, PhD** | Founder & CEO
- **John Nuss, PhD** | Chief Scientific Officer
- **Martin Auster, MD** | Chief Financial Officer
- **Chris Krueger, JD** | Chief Business Officer
- **Matt Cascino, MD** | VP, Clinical Development

### Guest Speakers and KOLs

- **Marty Pomper, MD, PhD** | Chair, Dept of Radiology, UT Southwestern
- **Ted Dawson, MD, PhD** | Professor of Neurology, John Hopkins University

**Disclosures:**

**Ted M. Dawson, MD, PhD:** Consulting: T.M.D. is compensated for his role as a consultant, advisor, or Director for FBIO Acquisition Corp L, a subsidiary of Fortress Biotech Inc.; Aevum Therapeutics, Inc.; Inhibikase Therapeutics Inc.; and Valted Seq Inc. Stock Ownership: T.M.D. owns stock, stock options, or royalty interests in Aevum Therapeutics, Inc.; American Gene Technologies International Inc.; FBIO Acquisition Corp L, a subsidiary of Fortress Biotech Inc.; AbbVie; Inhibikase Therapeutics Inc; Valted, LLC; Neuraly, Inc.; D & D Pharmatech; and Valted Seq Inc. Research Sponsorship: T.M.D has a sponsored research agreement with Sun Pharma Advanced Research and Aevum Therapeutics, Inc.

**Marty Pomper, MD, PhD:** University of Texas Southwestern Medical Center (employee); D&D Pharmatech (equity, research, royalties, consulting); PlenaryAI, Inc. (equity); z-alpha (equity, consulting); Lantheus Holdings (research, royalties); Novartis (consulting); Earli (equity, consulting)

# Internally Discovered Clinical-Stage Pipeline

## Addressing Major Autoimmune and Inflammatory Diseases with High Unmet Need

| Target | Program | Preclinical | Phase 1 | Phase 2 | Phase 3 | Next Anticipated Milestones |
|---|---|---|---|---|---|---|
| **NLRP3** *CNS-Penetrant* | VTX3232 | Parkinson's disease, obesity, and other neuroinflammatory diseases | | | | Initiate Ph 2a Parkinson's trial **H2 2024**<br>Initiate Ph 2a Obesity trial **H2 2024** |
| **NLRP3** *Peripheral* | VTX2735 | Cardiovascular and other systemic inflammatory diseases | | | | Phase 2 ready for CV indications |
| **S1P1R** | VTX002 | Ulcerative colitis | | | | Identify partner for Phase 3 trial |
| **TYK2** | VTX958 | Crohn's disease | | | | Phase 2 Crohn's data **mid 2024** |

# VTX958

## Phase 2 Crohn's Disease Program Update

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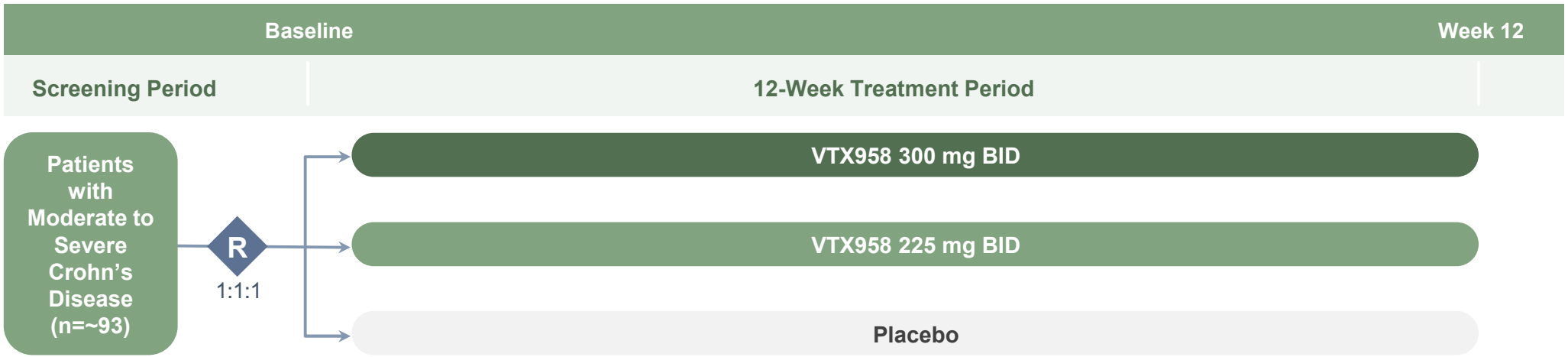
# VTX958 Phase 2 Crohn's Disease Trial

## Randomized, Placebo-Controlled Trial in Patients with Moderate to Severe Crohn's Disease




- **Protocol amendment implemented to streamline detection of a potential efficacy signal**
- **Primary Endpoints:** Change from baseline in mean CDAI score at Week 12
- **Secondary endpoints:** Proportion of patients achieving endoscopic response per SES-CD; Change in mean SES-CD score; proportion of patients achieving clinical remission and clinical response per CDAI; proportion of patients achieving PRO-2 remission
- Target enrollment changed to ~93 participants (previously ~132 participants); trial now closed to enrollment
- Randomization expected to complete in **Q1 2024; Topline data expected in mid 2024**
- Future capital commitment for VTX958 will be dependent on identification of a positive efficacy signal in the Phase 2 trial

SES-CD: Simple Endoscopic Score for Crohn's Disease; CDAI: Crohn's Disease Activity Index; PRO-2: Patient-Reported Outcome 2.

# VTX002

## Phase 2 OLE and Program Update

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# VTX002 Phase 2 Study in Moderate-to-Severe UC

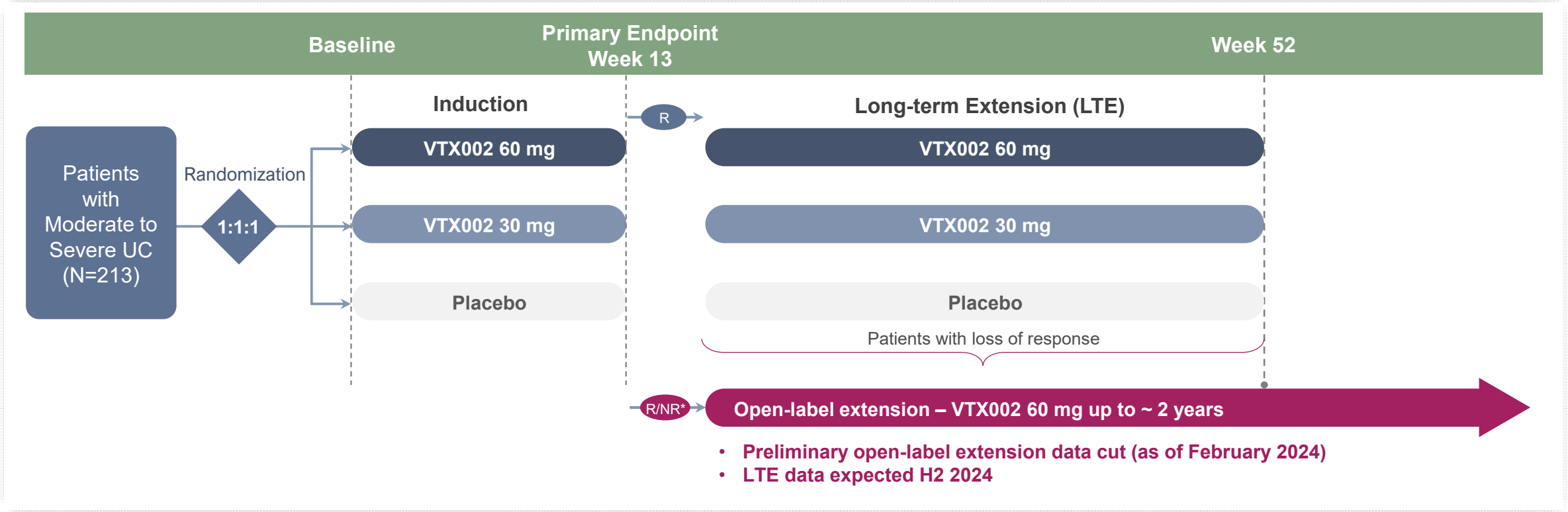
## Designed to Serve as the First of Two Pivotal Trials

**Key Eligibility Criteria**

- Patients with moderately to severely active UC as defined by the Modified (3-component) Mayo Score
- Insufficient response, loss of response, and/or intolerance to conventional or advanced therapies

**Endpoints**

- **Primary Endpoint:** Clinical remission at Week 13 as defined by the Modified Mayo Score
- **Key Secondary Endpoints:** Endoscopic improvement; symptomatic remission; histologic remission; endoscopic improvement-histologic remission




* Protocol version 1 study design. All patients had the option to roll-over regardless of response status. Subsequent protocol versions had patients with NR or loss of response only enter OLE
Note: NCT05156125. MMS: Modified Mayo Score; R: responder; NR: non-responder

# Overview of VTX002 Induction Data

## Robust Week 13 Clinical Remission with Differentiated Complete Endoscopic Remission

### Key Takeaways from VTX002 Week 13 Data

**Competitive week 13 clinical remission with differentiated endoscopic remission (MES=0)**

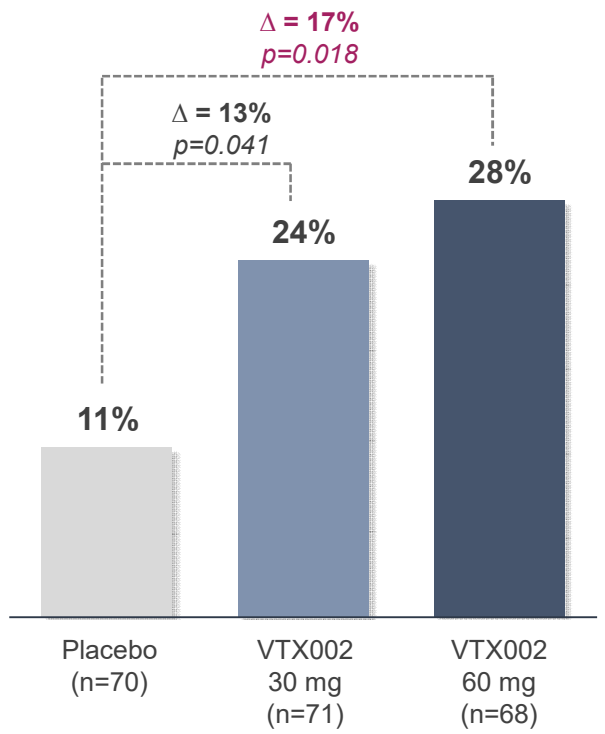
**Deep remission** (endoscopic and clinical remission), **symptomatic remission** and **histologic endoscopic mucosal improvement** rates further support clinical profile

Subgroup analysis demonstrated **differentiated clinical remission and endoscopic remission in patients with prior exposure to advanced therapies**

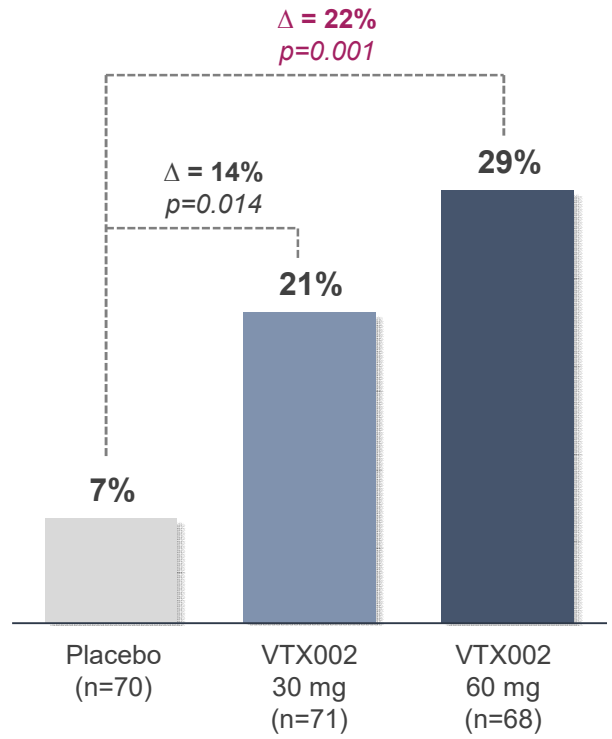
**Zero cases** of atrioventricular block, bradycardia, serious or opportunistic infections, or macular edema

**Baseline MMS 5 to 9 (N=209): Week 13**

**Clinical Remission (Primary)**




**Endoscopic Remission (MES=0)**



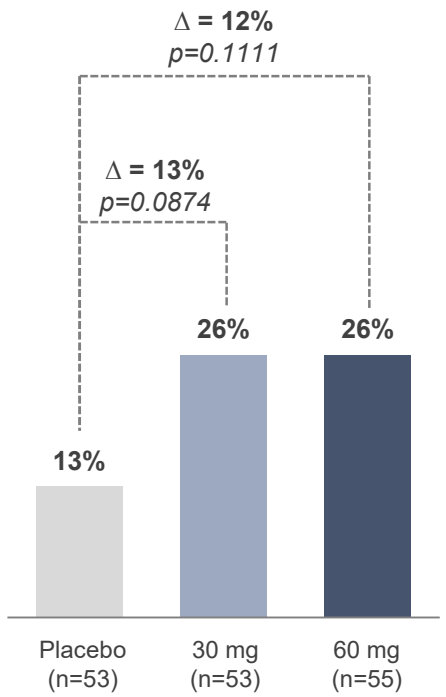

Clinical remission by modified Mayo Score (MMS) is defined as stool frequency subscore = 0 or 1, rectal bleeding subscore = 0, and endoscopic subscore ≤ 1 (excluding friability). Endoscopic remission is defined as a Mayo endoscopic subscore of 0. P-value for testing the treatment difference is based on Cochran-Mantel-Haenszel test adjusted for prior use of advanced therapies, baseline corticosteroid use and baseline disease activity. Full analysis set with non-responder imputation. Source: Ventyx data on file

# Induction Subgroup Analysis: Advanced Therapy Prior Use

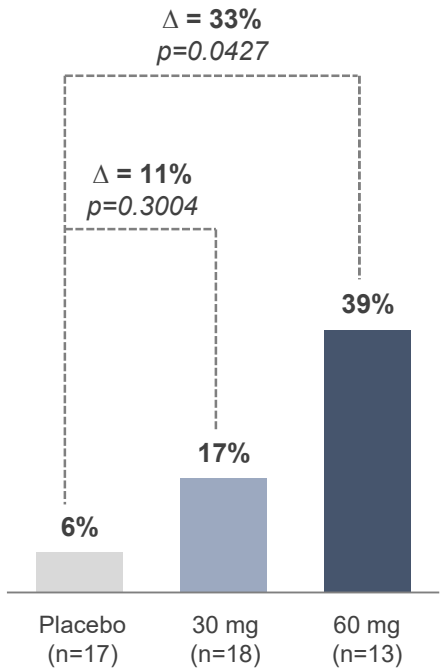
## Clinical Remission and Endoscopic Remission at Week 13

### Clinical Remission

#### Advanced Therapy Naïve

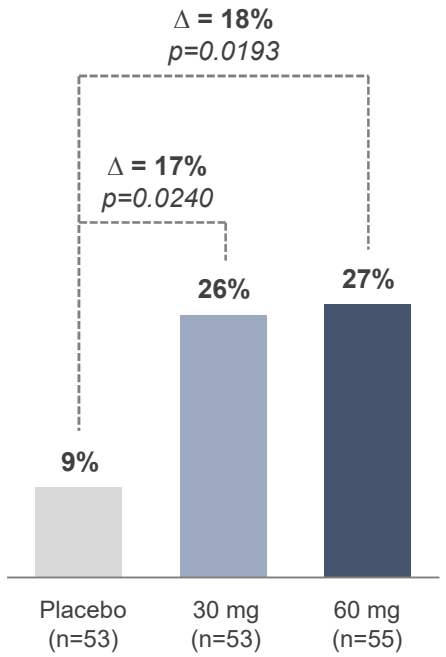



#### Advanced Therapy Experienced

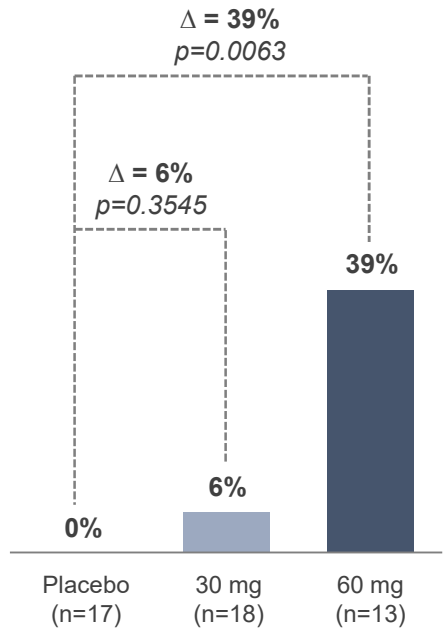



### Endoscopic Remission

#### Advanced Therapy Naïve




#### Advanced Therapy Experienced



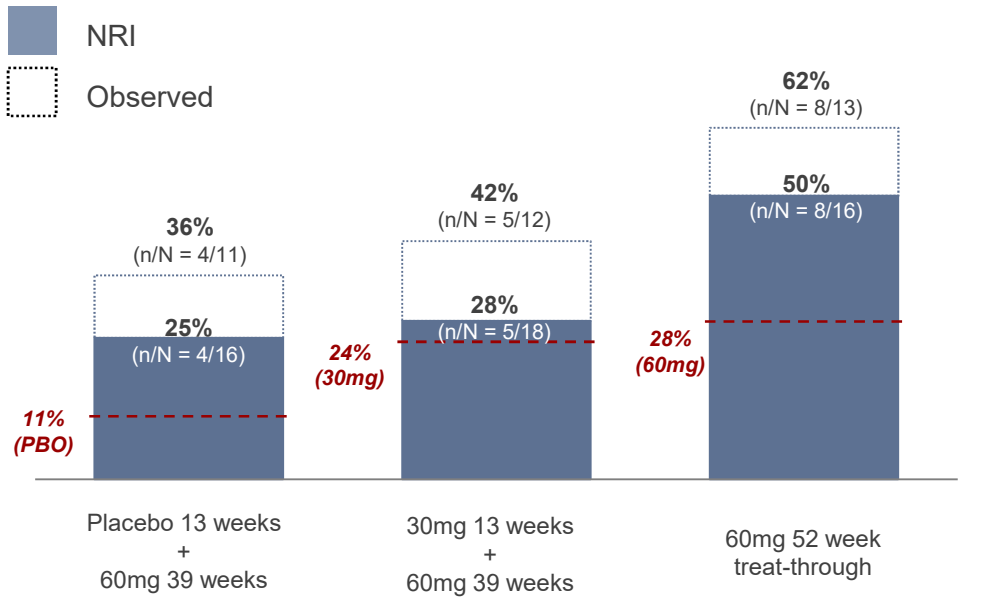

Clinical remission by modified Mayo Score (MMS) is defined as stool frequency subscore = 0 or 1, rectal bleeding subscore = 0, and endoscopic subscore ≤ 1 (excluding friability). Endoscopic remission is defined as a Mayo endoscopic subscore of 0. P-value for testing the treatment difference is based on Cochran-Mantel-Haenszel test adjusted for prior use of advanced therapies, baseline corticosteroid use and baseline disease activity. Full analysis set with non-responder imputation. Source: Ventyx data on file

# Preliminary Open-Label Extension Data

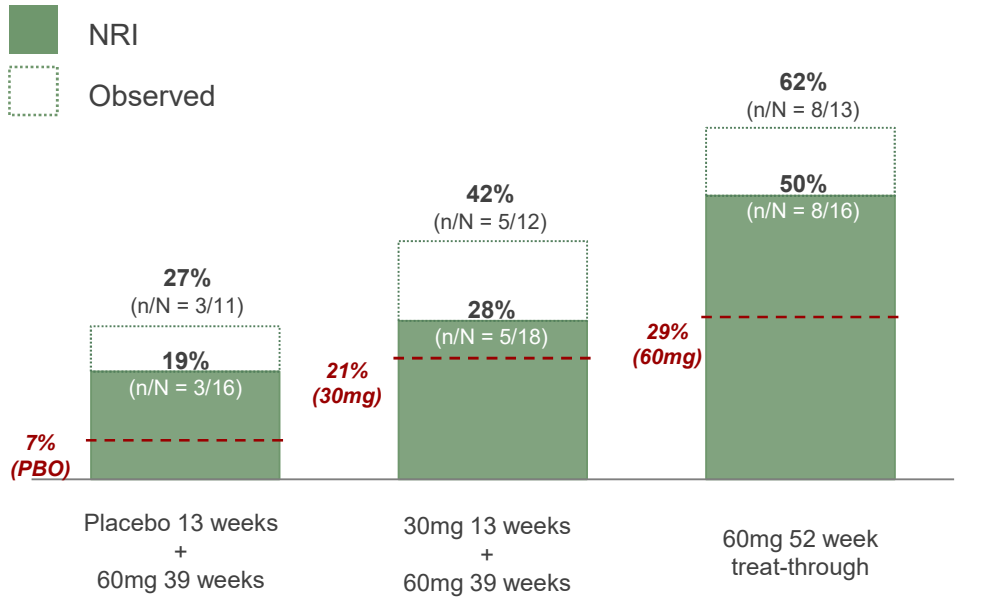
## Further improvement in clinical and endoscopic remission rates at OLE week 39

*% absolute endpoint rate (clinical or endoscopic remission) in induction dose arm at 13 weeks*

### % Clinical Remission at OLE Week 39[1] by Induction Dose Arm




### % Endoscopic Remission[2] at OLE Week 39[1] by Induction Dose Arm




**At least half (NRI) of patients in 60mg treat-through group reach clinical remission or endoscopic remission at week 52**

Note: NRI = non-responder imputation; participant discontinuations are assumed to be non-remitters

[1] Irrespective of the clinical response at the end of the 13-week induction phase; VTX002 60mg / 60mg represents 52 weeks treat-through efficacy; other groups received 60mg for 39 weeks post- induction; [2] MES =0; Source: Ventyx data on file.

# Endoscopic Remission is a Consensus Long-Term Treatment Goal

## Current therapeutic outcomes remain disappointing: VTX002 has demonstrated the potential to set a new bar

### Current Endoscopic Remission Outcomes

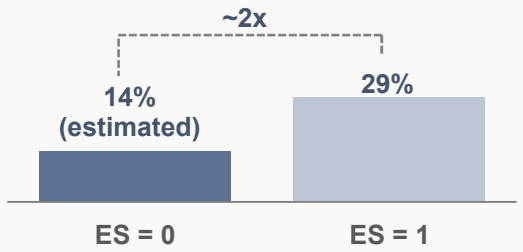
**1** **The Vast Majority of Patients on Advanced Therapy Fail to Reach Endoscopic Remission, Particularly Within the Induction Period[1]:**

**82-95%**

*Absolute % patients in Phase 3 for advanced UC agents that fail to achieve MES=0 at induction*

**2** **Achievement of Endoscopic Remission (MES=0) vs. Mild Endoscopic Activity (MES=1) is Associated with Improved Long-Term Patient Outcomes[2]:**

**12-month risk of clinical relapse**
(meta-analysis of 17 studies):




**3** **Achievement of Endoscopic Remission (MES=0) is Recognized in STRIDE II[3] Guidelines as an Aspirational Target of Long-Term Treatment:**

**MES=0**

- **Lower risk of disease recurrence**
- **Decreased steroid use**
- **Lower rate of surgical intervention & hospitalization**
- **Superior patient-reported outcomes**

### VTX002 Profile

#### Induction Data

- **Competitive clinical remission** and **differentiated endoscopic remission**
- Differentiated clinical and endoscopic **outcomes in prior advanced therapy subgroup**

#### OLE Data

- Clinical remission and endoscopic remission rates at **OLE week 39 further differentiate VTX002**
- **Differentiated endoscopic remission rates** achieved in 52-week 60mg VTX002 treat-through group
- Competitive rates of ***sustained*** **clinical and endoscopic remission:**
  - At least 38% (NRI) of patients in 60mg 52wk treat-through arm were in clinical remission at both week 13 and week 52
  - Patients in clinical remission were also in endoscopic remission

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[1] Based on analysis of Phase 3 trials for biologic and oral approved advanced agents; [2] Source: Yoon et al. Gastroenterology 2020;159(4):1262-1275.e7; [3] Source: Turner et al. Gastroenterology 2021;160:1570–1583

# VTX002 OLE Conclusions and Program Status

## Ventyx to Identify Partner or Other Source of Nondilutive Financing for Phase 3

- **OLE data continue to support the differentiated profile of VTX002 in ulcerative colitis**
- **VTX002 is Phase 3 ready (clinical, CMC, regulatory)**
  - End of Phase 2 meeting scheduled in Q2 2024
  - Phase 2 trial expected to serve as the first of two pivotal trials; single Phase 3 required for registration*
- **Ventyx to identify partner or other source of nondilutive financing for Phase 3**
  - New capital allocation priorities favor NLRP3 programs
  - Currently no additional internal spend planned for VTX002 other than to support ongoing Phase 2 LTE/OLE

*Pending outcome of planned discussions with regulators.

# NLRP3 Inhibition

## Broad Potential in Inflammatory Diseases

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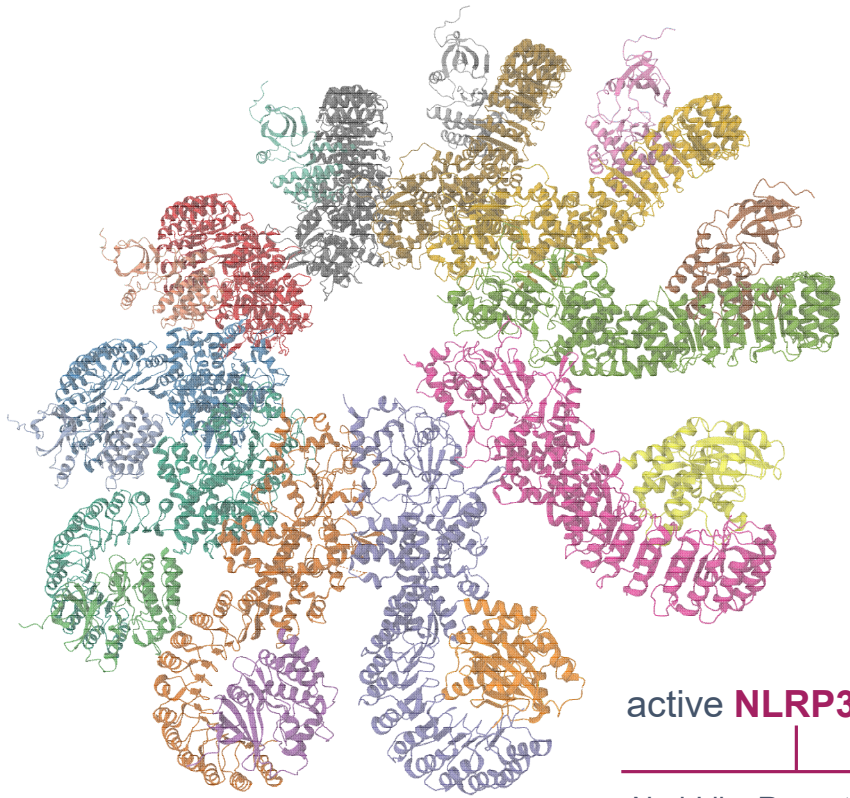
# NLRP3 Inflammasome: A Key Component of Innate Immunity

## Dysregulation Linked to a Broad Range of Inflammatory Diseases

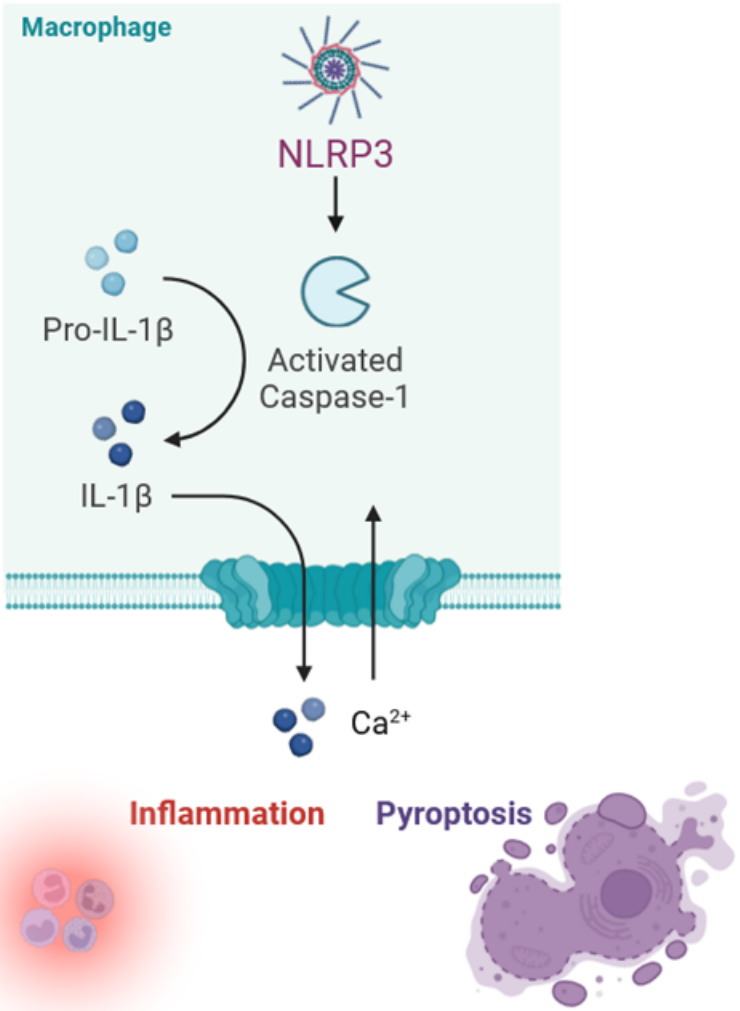


active **NLRP3** inflammasome disk

Nod-Like Receptor family
Pyrin domain containing 3

**Inflammasomes** are activated by molecular hallmarks of infection or cellular injury

**NLRP3** mediates release of proinflammatory cytokines **IL-1β** and **IL-18** and drives a form of cell death called **pyroptosis**



# NLRP3 Is a High Value Therapeutic Target

## Broad Potential Across Systemic and CNS Inflammatory Disease

### VTX2735

### Systemic Diseases

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

- Cardiovascular/Metabolic
- Dermatologic
- Rheumatic
- CAPS (FCAS)
- Other orphan indications

### VTX3232

### Neuroinflammatory Diseases

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

- Parkinson's Disease
- Multiple Sclerosis
- Alzheimer's Disease
- Obesity

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CNS: Central nervous system. CAPS: Cryopyrin-associated periodic syndromes. FCAS: Familial cold autoinflammatory syndrome

# VTX2735

## Peripheral NLRP3 Inhibitor

## Phase 2 CAPS (FCAS) Trial Results

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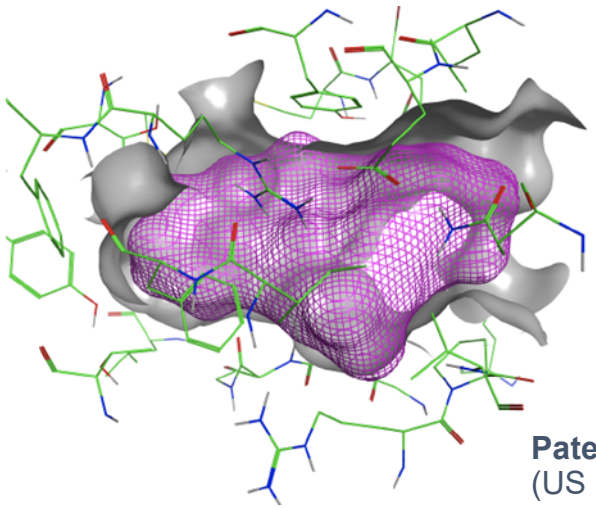
# VTX2735: A Potent & Selective Peripheral NLRP3 Inhibitor

## Phase 2 Ready for Systemic Inflammatory Diseases

### Highly Potent & Selective

- hu WB $IC_{50}$ (IL-1β) = 80 nM
- No inhibition of other inflammasomes



**Patent granted**
(US Pat. No. 11,603,375)

### Nonclinical & Phase 1 Package

- Demonstrated PD and *in vivo* efficacy in rodent models
- High exposures & target coverage achieved in Phase 1
- Promising clinical safety profile
  - No signals that raise safety concerns that require further nonclinical study for genetox, safety pharmacology and phototoxicity
  - Chronic tox studies initiated, to finish EOY
  - Current tox data support 3 months of human dosing
- Potent inhibitor in PBMC from CAPS (FCAS) patients

**Phase 2 proof-of-concept study in CAPS patients (FCAS) completed**

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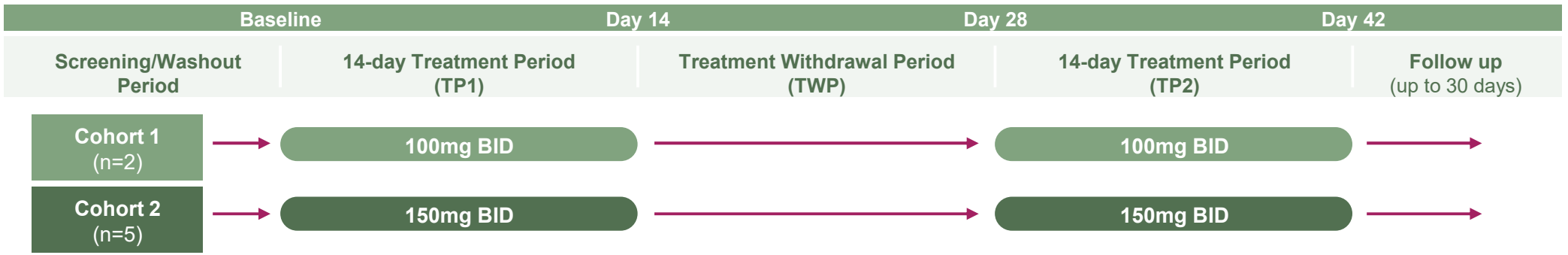
Source: Ventyx internal data. CAPS: Cryopyrin-associated periodic syndromes. FCAS: Familial cold autoinflammatory syndrome. WB: whole blood

# VTX2735 Phase 2 Open-Label Trial in CAPS (FCAS)

## Trial Design and Participants

- **CAPS** is an ultra rare condition driven by **excess NLRP3 activity; FCAS is the most common subtype**
- Following washout of SoC, VTX2735 dosed for 14 days in two treatment periods (TP1 and TP2, 28 days total)
- **Key endpoints:** safety/tolerability and improvement in Key Symptom Score (**KSS**, mean of 5 symptom scores)
  - **Pharmacodynamic assessments:** hsCRP; acute phase reactants (SAA, IL-1α, IL-1β, IL-6, and IL-18)
- **7 participants enrolled** (diverse NLRP3 mutations, prior SoC therapies, and symptoms)
  - 5 participants completed the trial; 1 withdrew consent after TP1 and 1 withdrew due to lack of efficacy



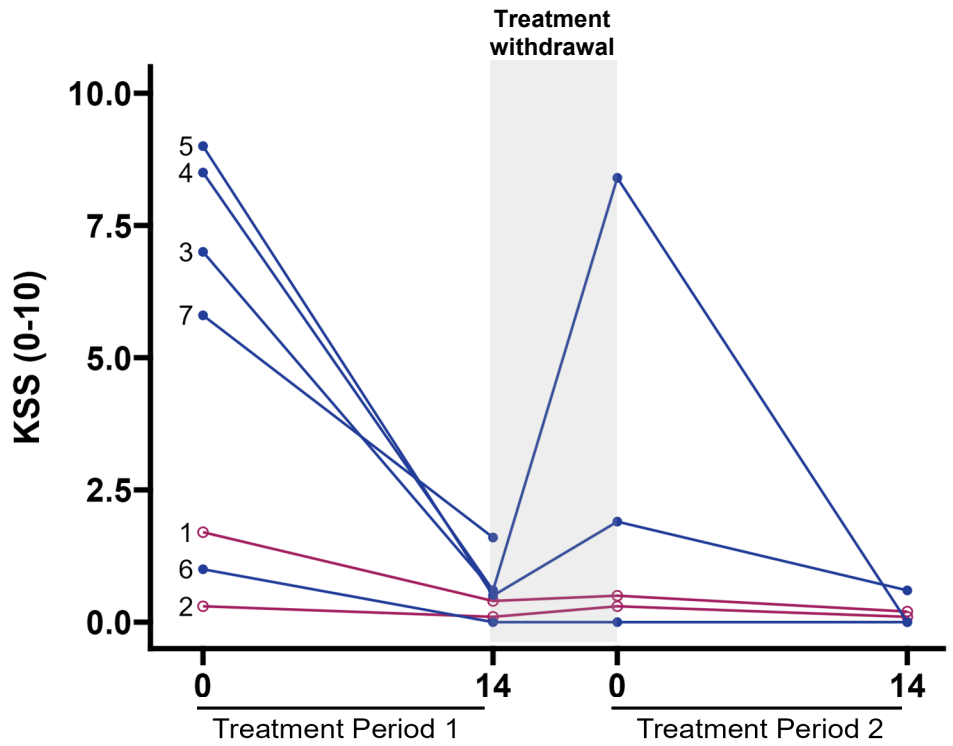

Source: Ventyx data on file.

# Treatment with VTX2735 Drives Reductions in Disease Activity

## Disease Activity as Assessed by Key Symptom Score (KSS) and General Well-Being

### Key Symptom Score (0-10)*

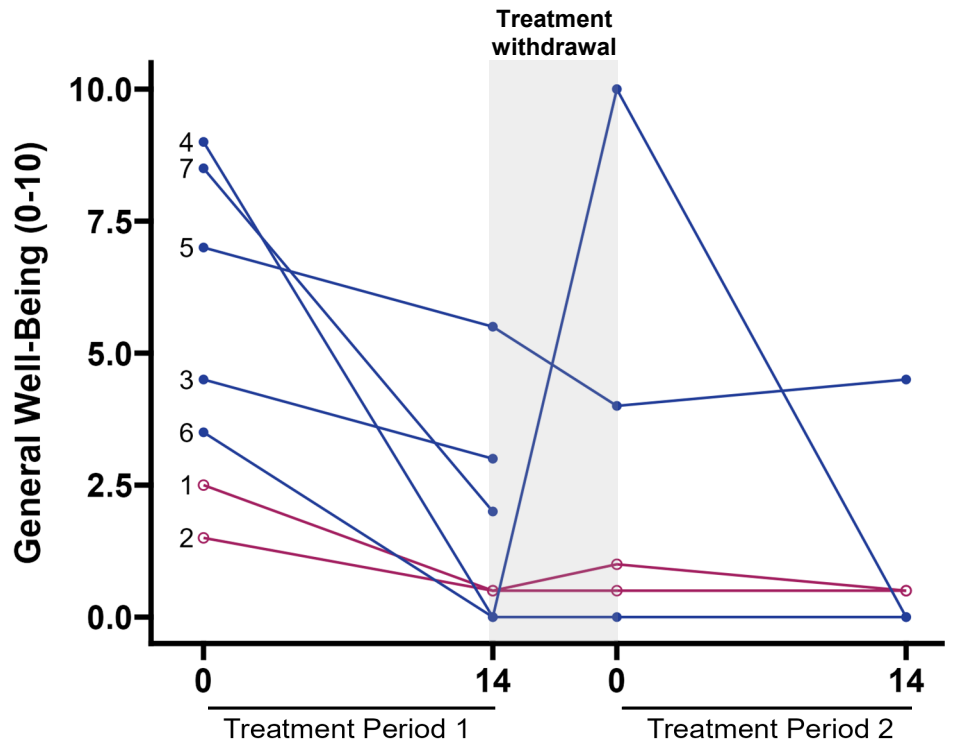
*Daily mean of five symptom scores*




**Mean 85% reduction during Treatment Period 1**

### General Well-Being (0-10)*

*"Considering all the ways FCAS affects you, please rate how you are doing"*



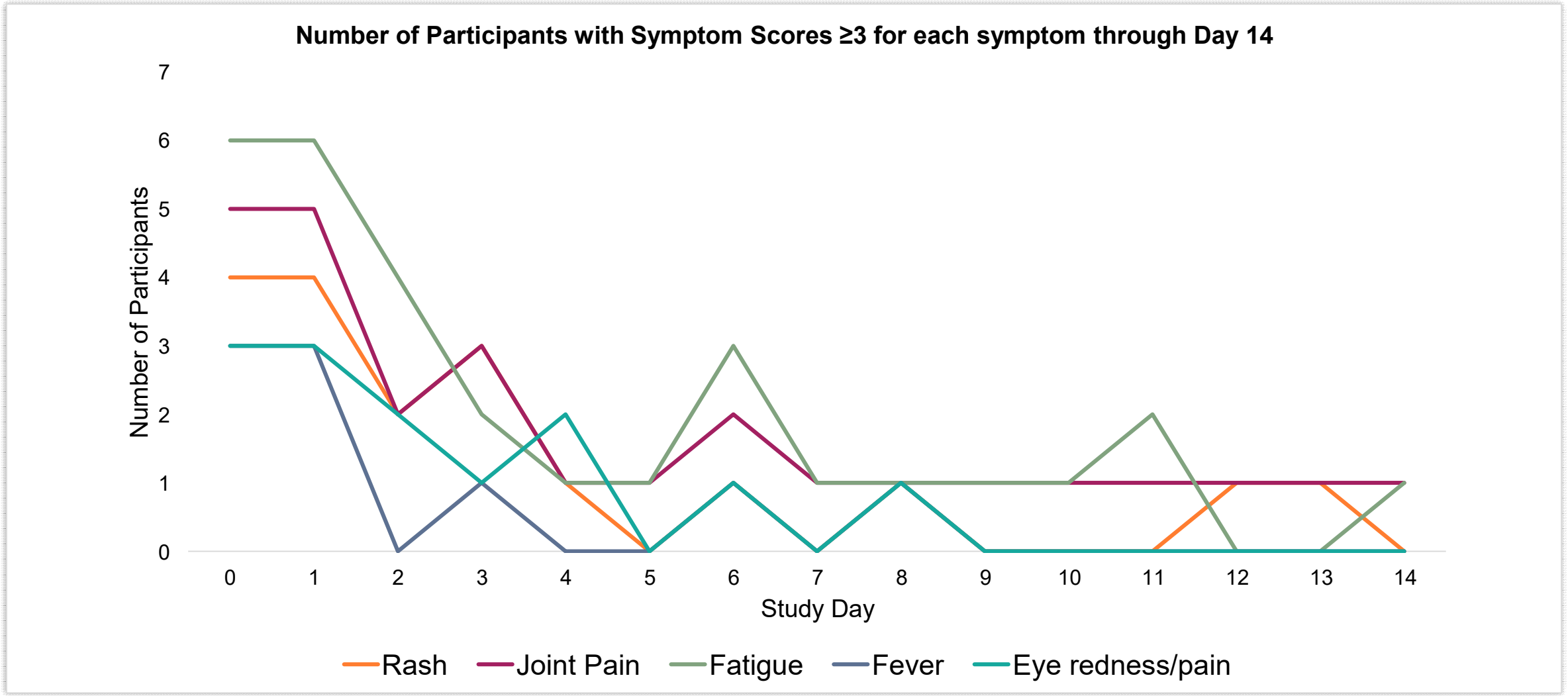

**Mean 68% reduction during Treatment Period 1**

100 mg BID — 150 mg BID

Source: Ventyx data on file (07 March 2024). *Note: One participant did not complete Treatment Period 1; the final measurement prior to study discontinuation is reported.

# VTX2735 Effects on Disease Activity

## Improvement in All CAPS Symptoms During First Week of Treatment with VTX2735




Source: Ventyx data on file (07 March 2024).

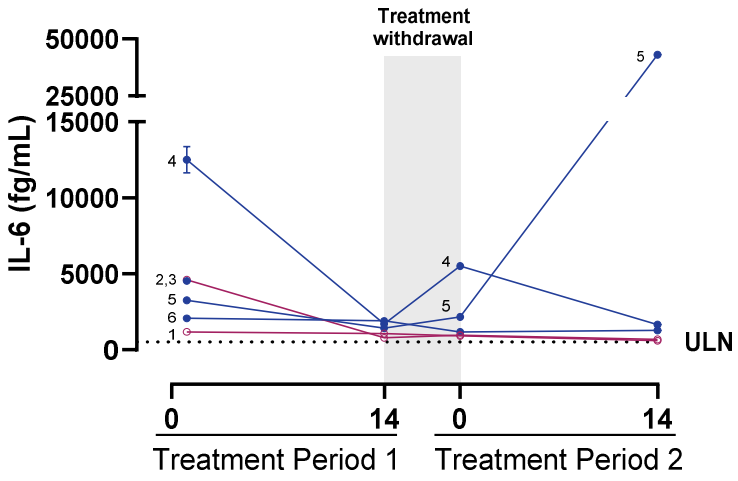
# VTX2735 Biomarker Changes

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

- The pleiotropic cytokine **IL-6** induces acute-phase reactant proteins, including C-reactive protein (**CRP**) and Serum amyloid A (**SAA**)
- Treatment with VTX2735 **reduced plasma IL-6, hsCRP, and SAA** in patients with elevations at baseline, consistent with reductions in disease activity
  - Lack of baseline elevations in some patients is likely attributable to long half-life of SoC antibodies (canakinumab)

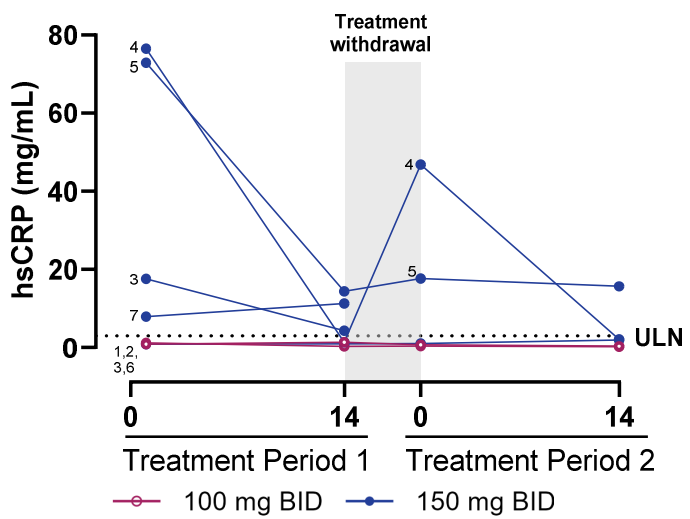
**IL-6**

*Interleukin 6*



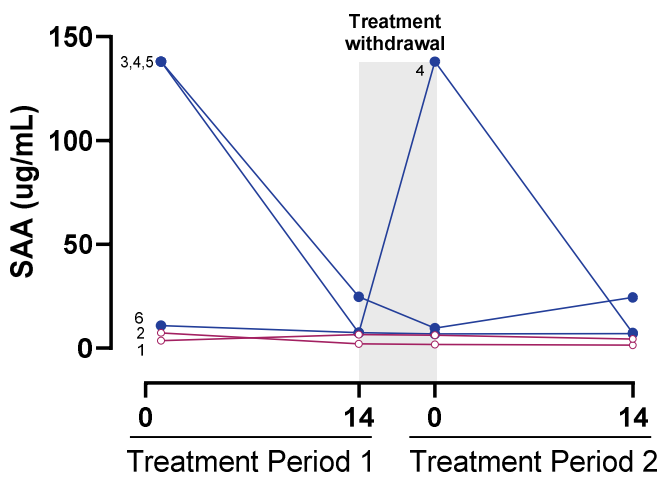

**hsCRP**

*High-sensitivity C-reactive Protein*




**SAA**

*Serum amyloid A*




Source: Ventyx data on file. *Note: One participant did not complete Treatment Period 1; the final measurement prior to study discontinuation is reported. No IL-6 or SAA data available for Participant No. 7

# VTX2735 Was Well Tolerated

## All Adverse Events Were Mild or Moderate and Resolved Without Treatment Interruption

### Related AEs

| AE | Grade | Relationship | Action | Outcome | SAE |
|---|---|---|---|---|---|
| Activated partial thromboplastin time prolonged | Grade 1 | Related | Dose not changed | Recovered/Resolved | No |
| Anxiety | Grade 1 | Related | Dose not changed | Recovered/Resolved | No |
| Blood phosphorus increased | Grade 1 | Related | Dose not changed | Recovered/Resolved | No |
| Prothrombin time/INR prolonged | Grade 1 | Related | Dose not changed | Recovered/Resolved | No |
| Pyrexia | Grade 1 | Related | Dose not changed | Recovered/Resolved | No |

### Grade 2 or Higher AEs

| AE | Grade | Relationship | Action | Outcome | SAE |
|---|---|---|---|---|---|
| Gastroenteritis | Grade 2 | Not related | Dose not changed | Recovered/Resolved | No |
| Left rotator cuff tear | Grade 2 | Not related | Dose not changed | Recovered/Resolved | No |

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Source: Ventyx data on file.

# Conclusions from the Phase 2 Trial of VTX2735 in FCAS Patients

## Clinical Proof of Concept Achieved in CAPS Patients

- **VTX2735 showed clinically-meaningful effects on disease activity and relevant biomarkers**
- **VTX2735 was well-tolerated**
  - All adverse events were mild or moderate and resolved without treatment interruption
- **These data represent a major milestone for VTX2735 and for NLRP3 inhibition**
  - **Dr. Hal Hoffman (UCSD):** “Results similar to what we have seen in IL-1 inhibition studies” (Ilaris, Kineret, etc.); particularly impressive in a treatment-experienced population

# VTX2735 is a Phase 2 Ready Peripheral NLRP3 Inhibitor

## Highly Potent & Selective

- Structurally unique, selective inhibitor of NLRP3
- Potent inhibitor of NLRP3 with $IC_{50}$ = 80 nM in human whole blood assay
- Highly potent vs. CAPS mutation variants

## Biologic-like Activity in CAPS Trial

- Concentration dependent suppression of IL-1β *ex vivo*
- Reduction in hsCRP and other inflammation markers (IL-6, SAA, neutrophils)
- Clinically-meaningful benefits observed in CAPS patients

## Promising Safety Profile

- No CYP, hERG or transporter interactions
- No toxicological signals of concern
- Well-tolerated in all SAD/MAD dose groups and Phase 2 CAPS trial

## Phase 2 Ready

- IP position secure; patent issued (US Pat. No. 11,603,375)
- Multi-kilo API production completed
- Extended-release dosing form expected Q3 2024

# VTX3232

## CNS-Penetrant NLRP3 Inhibitor

## Phase 1 Trial Results

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# VTX3232: Designed to Achieve Disease-Modifying CNS Exposures

## Phase 2 Ready for Neuroinflammatory Diseases

**Highly Potent and Selective**

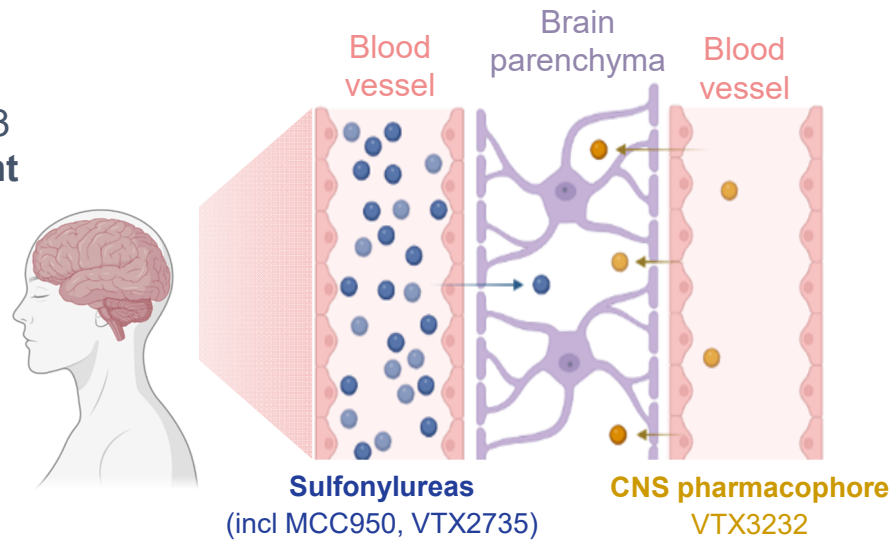
- hu WB $IC_{50}$ (IL-1β) = **15 nM**
- hu Microglia $IC_{50}$ (IL-1β) = **2.7 nM**
- No inhibition of other inflammasomes

**Optimal CNS-drug properties in Phase 1**

- Promising safety & tolerability through 14-day MAD
- Near-equal CNS partitioning; **human Kp,uu = 0.5**
- T½ = ~17 h with high free-drug fraction
- **20-40 mg QD exceeds CSF IL-1β $IC_{90}$ for 20-24 h**
- Robust effects on inflammatory biomarkers

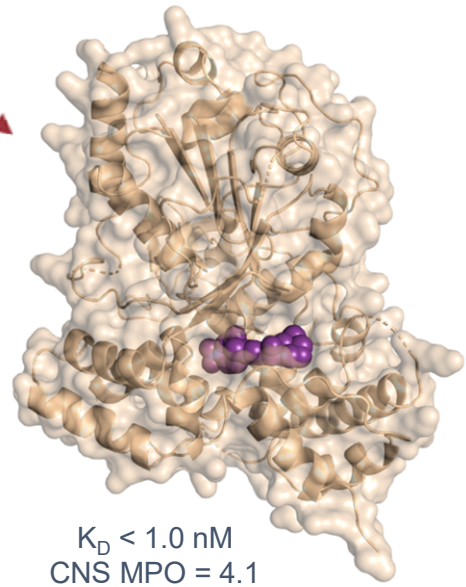
Sulfonylurea class of NLRP3 inhibitors have **poor inherent BBB permeability**

**High systemic doses** required to achieve CNS efficacy




**VTX3232** is rationally-designed for **CNS efficacy** without high peripheral exposures

**Rapid equilibration** across BBB to reach microglial target cells

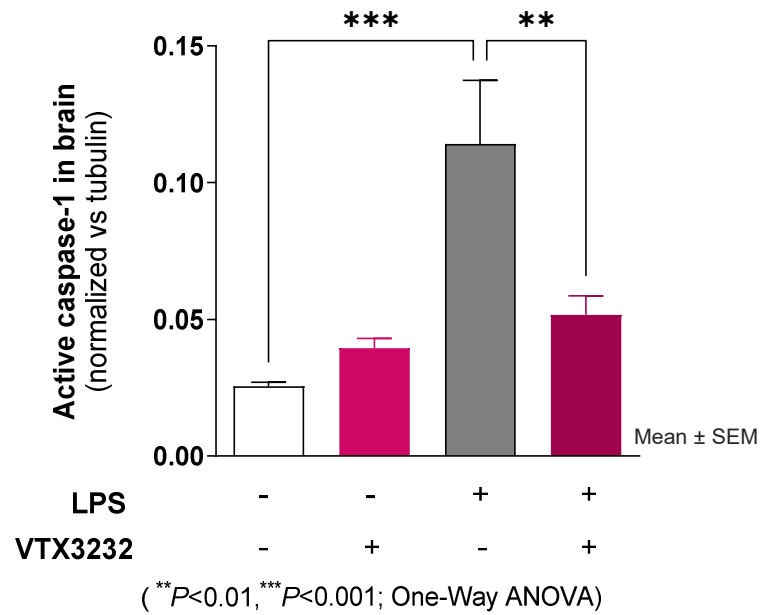


$K_D$ < 1.0 nM
CNS MPO = 4.1

Source: Ventyx internal data. BBB, blood brain barrier; CNS, central nervous system, Kp,uu, partition coefficient; MPO, multiparameter optimization. Images created with BioRender.

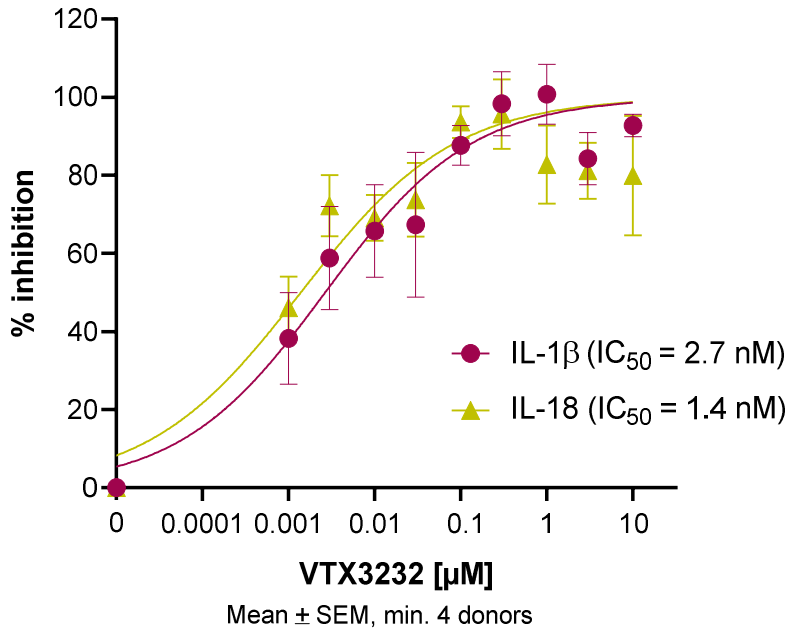
# VTX3232 Efficacy In Neuroinflammation Models

## Mouse Neuroinflammation Model




Inhibition of caspase-1 activation (directly downstream of NLRP3)

## LPS-Primed Human Microglia



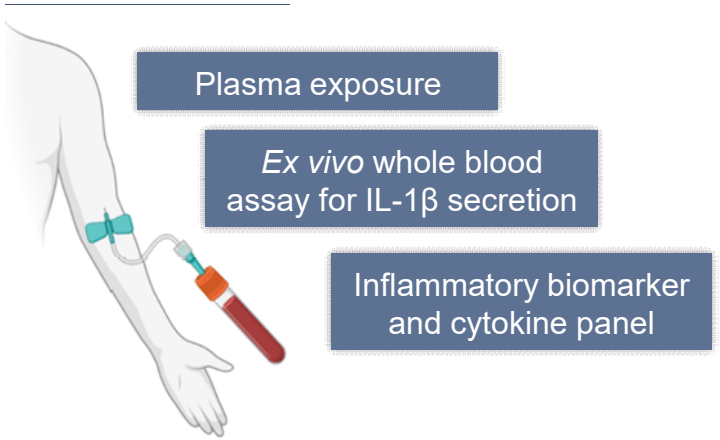

Potent inhibition of induced IL-1β & IL-18, selective vs TNFα

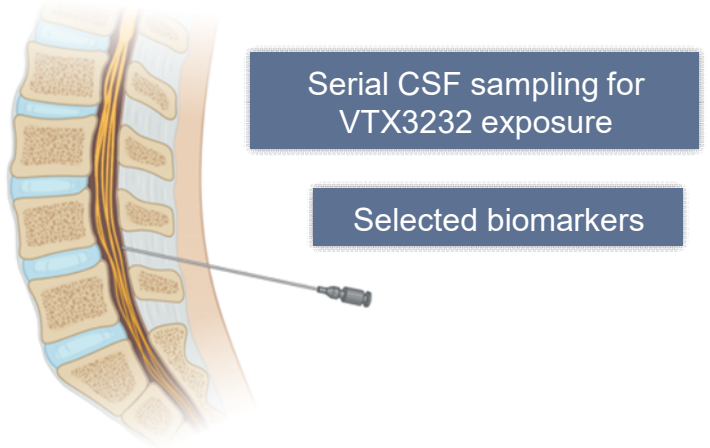
**VTX3232 activity translates to CNS-relevant assays and models**

Source: Ventyx internal data. CNS: central nervous system.

# VTX3232 Phase 1 SAD and 14-Day MAD Trial in Healthy Volunteers

| Phase 1 SAD and MAD Study Goals | Status |
|---|---|
| SAD and MAD to assess safety, tolerability and exposure | **Complete** |
| Ex vivo pharmacodynamic assessment of IL-1β inhibition* | **Complete** |
| Separate cohorts for VTX3232 exposure in CSF** | **Complete** |
| Plasma and CSF biomarkers | Ongoing |
| Relative bioavailability of VTX3232 tablets | **~100%** |
| Food effect study | **No food effect** |




*LPS/ATP stimulation of huWB from treated subjects in MAD
**CSF exposure is a surrogate for drug free-fraction in the brain

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# VTX3232 Safety Assessment

## All Adverse Events Considered Mild or Moderate (Phase 1 MAD Cohorts)

| | | VTX3232 (MAD) | | | | |
|---|---|---|---|---|---|---|
| **Treatment Emergent AEs** | **Placebo** (n=10) | **1 mg** (n=6) | **3 mg** (n=6) | **10 mg** (n=6) | **20 mg** (n=6) | **40 mg** (n=6) |
| Vomiting | 1 (10%) | - | - | - | - | - |
| Conjunctivitis | 1 (10%) | - | - | - | - | - |
| Constipation | 1 (10%) | 1 (16.7%) | - | - | - | - |
| Covid-19 | 1 (10%) | - | - | - | - | 1 (16.7%) |
| Viral Syndrome | 1 (10%) | - | - | - | - | - |
| Gastroenteritis | - | - | - | 1 (16.7%) | - | - |
| Contact dermatitis | - | - | - | - | 1 (16.7%) | - |
| Dry skin on legs | - | - | - | - | 1 (16.7%) | - |
| Lightheaded | - | - | - | - | - | 1 (16.7%) |
| Headache | - | - | - | - | - | 1 (16.7%) |
| Nausea | - | - | - | - | - | 1 (16.7%) |
| Drowsiness | - | - | - | - | - | 1 (16.7%) |

Note: MAD CSF cohorts are excluded in the table above as the safety profile in these cohorts is obscured by AEs related to indwelling spinal catheters.

### Safety Findings

- VTX3232 was **well tolerated** in Phase 1 SAD/MAD trial
- All treatment emergent AEs considered mild or moderate (CTCAE Grade 1 or 2)
- **No dose-limiting toxicities** observed
- Safety profile supports wide therapeutic window

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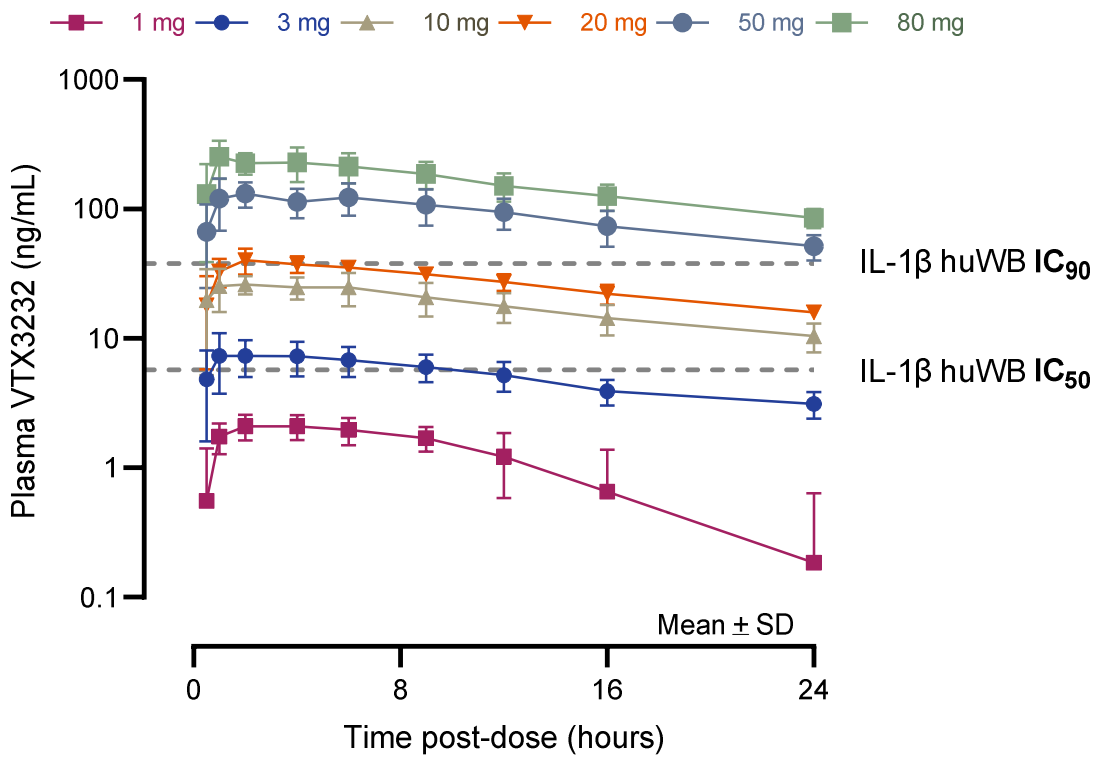
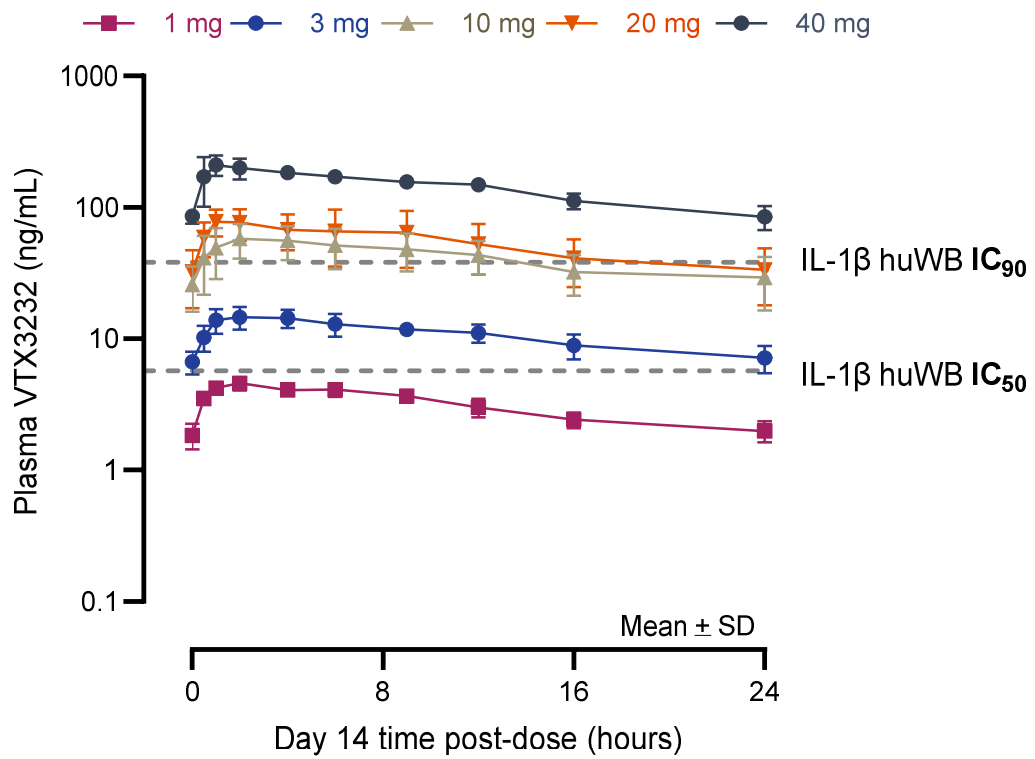
Source: Ventyx internal data.

# VTX3232 Phase 1 SAD and 14 Day MAD Pharmacokinetics

## Single Ascending Dose




## Multiple Ascending Dose



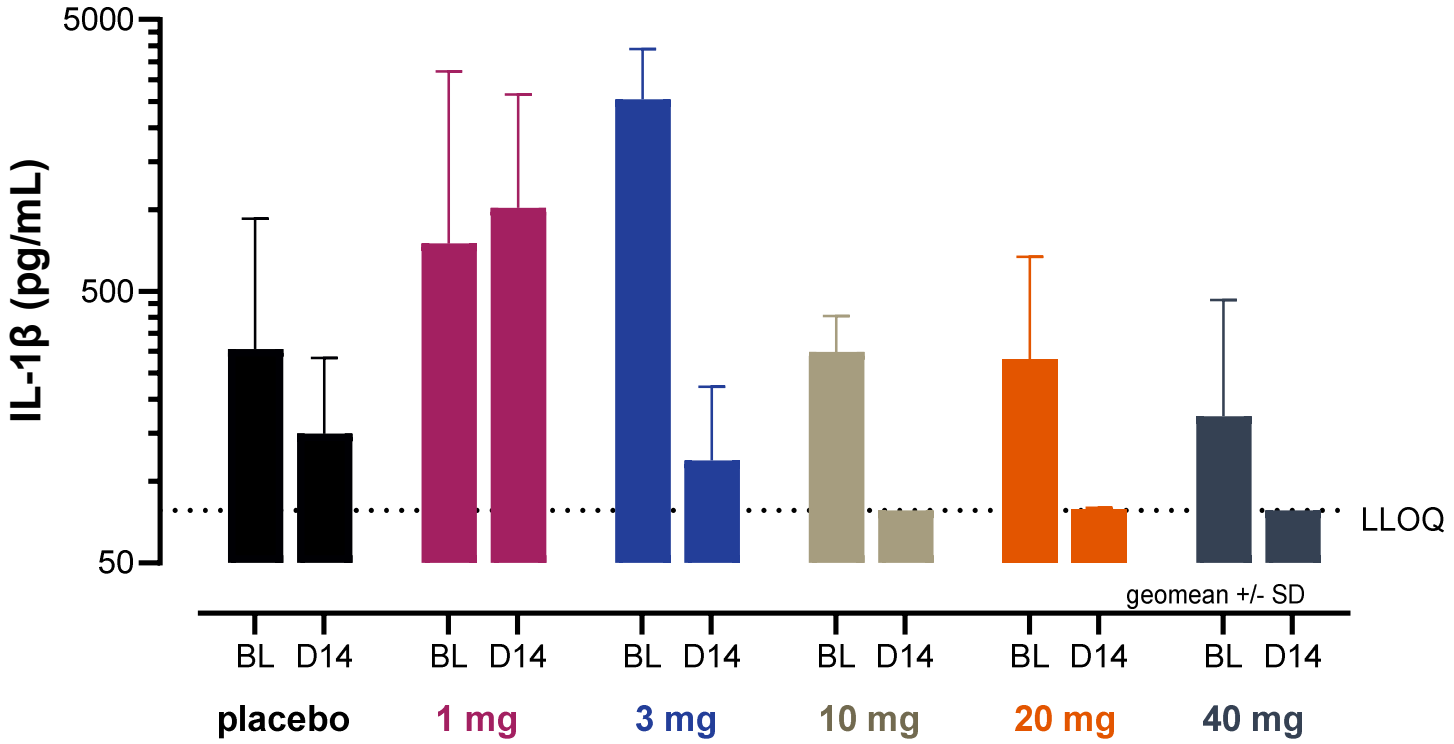

Dose-related, linear exposure from 1 mg to 80 mg

**3 mg QD** achieves **24 h IL-1β $IC_{50}$** coverage

Source: Ventyx internal data.

# VTX3232 Whole Blood *Ex Vivo* Stimulation Assay

## Potent Target Engagement Demonstrated At and Above 3 mg QD




1. Lower Limit of Quantitation (LLOQ)= 78 pg/mL. All subjects below LLOQ were assigned a value of 78 pg/mL.
2. Day 14 pre dose (D14). Pre dose baseline (BL).

**Data Summary**

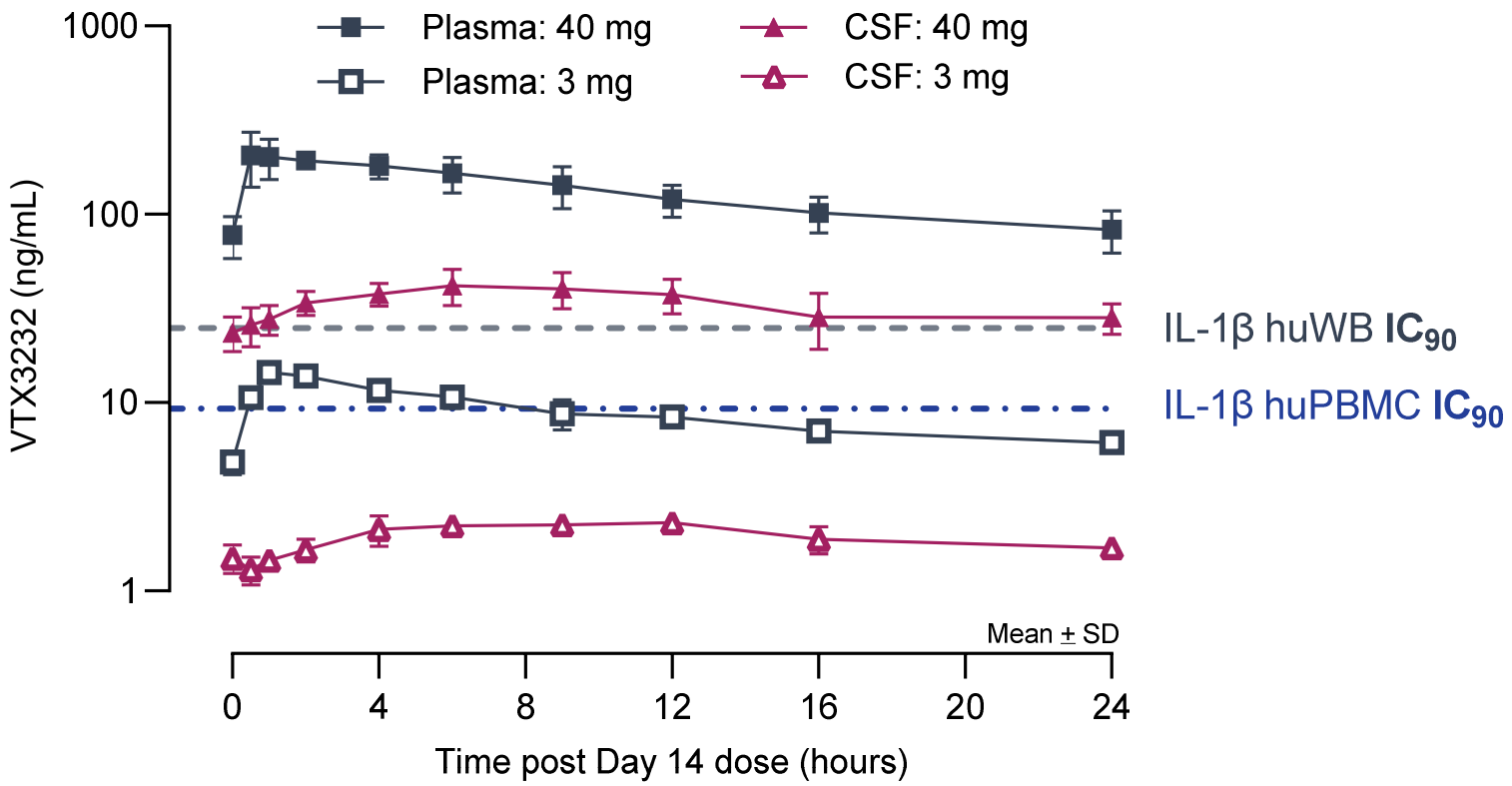
Blockade of NLRP3 mediated IL-1β is maintained at Day 14 with repeat dosing

Maximal inhibition achieved at doses of 10 mg QD and higher

Source: Ventyx internal data.

# VTX3232 Pharmacokinetics in Cerebrospinal Fluid (CSF)

## Matched Plasma & CSF Exposure in MAD Cohorts




## Data Summary

VTX3232 achieves comparable exposures in both plasma and CSF

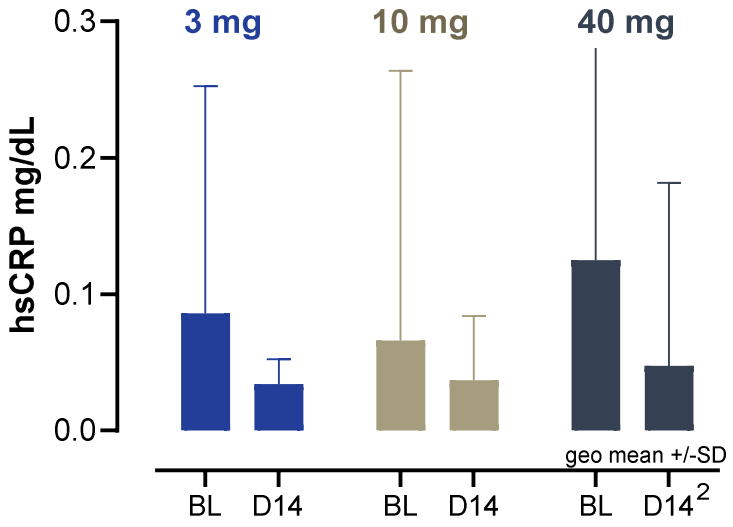
40 mg QD **exceeds CSF $IC_{90}$ for 24 h**, achieving robust target coverage for NLRP3 in microglia for neuroinflammatory conditions

Source: Ventyx internal data.

# VTX3232 Effects on Inflammatory Biomarkers

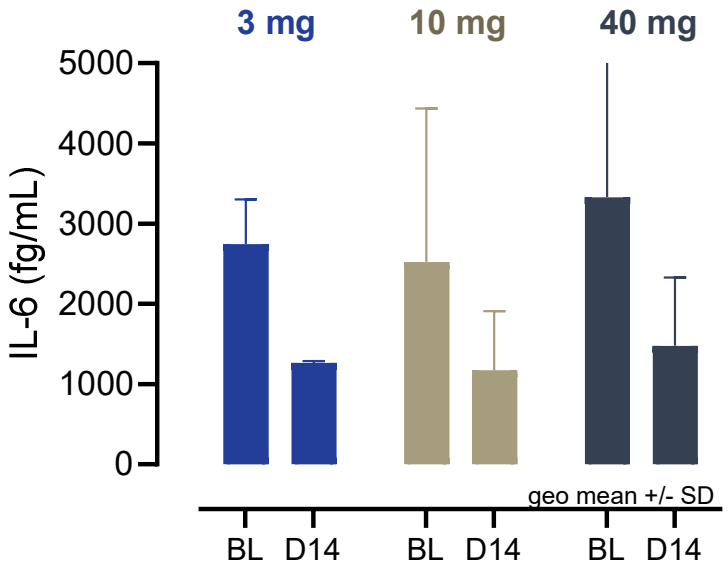
## Reduction in hsCRP and IL-6 Comparable to that Achieved by Canakinumab* (IL-1β mAb)

### Plasma hsCRP

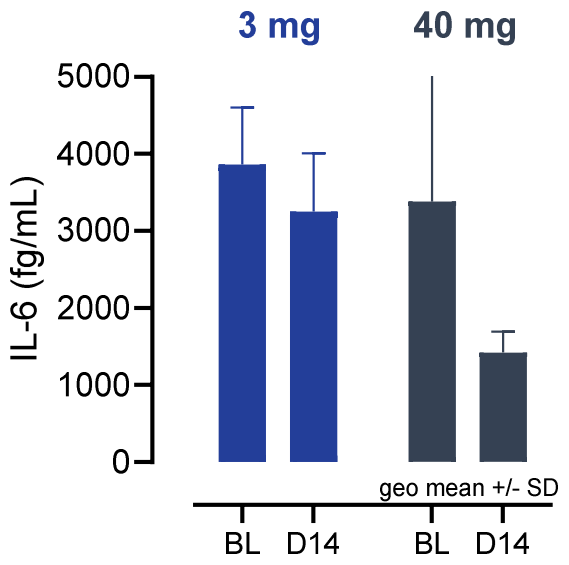



Systemic inflammation biomarker hsCRP lowered by as much as 55%

### Plasma IL-6




### CSF IL-6




IL-6 lowered by as much as 46% in plasma

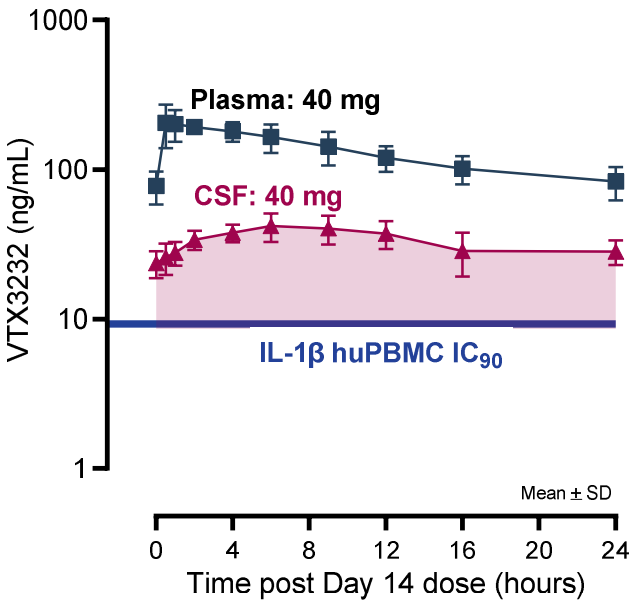
*Canakinumab: 35-40% hsCRP and IL-6 reduction based on literature reported values for canakinumab[1]

1. Ridker PM, MacFadyen JG, Everett BM *et al.*. *Lancet* 2018; 391:319-28; Ridker PM, Libby P, MacFadyen JG *et al. Eur Heart J.* 2018; 39:3499-507.
2. Day 14 pre dose samples not available for 40mg cohort. Data 2hr post dose displayed.
Source: Ventyx internal data. BL: pre-dose baseline. D14: Day 14 pre-dose samples, unless otherwise noted.

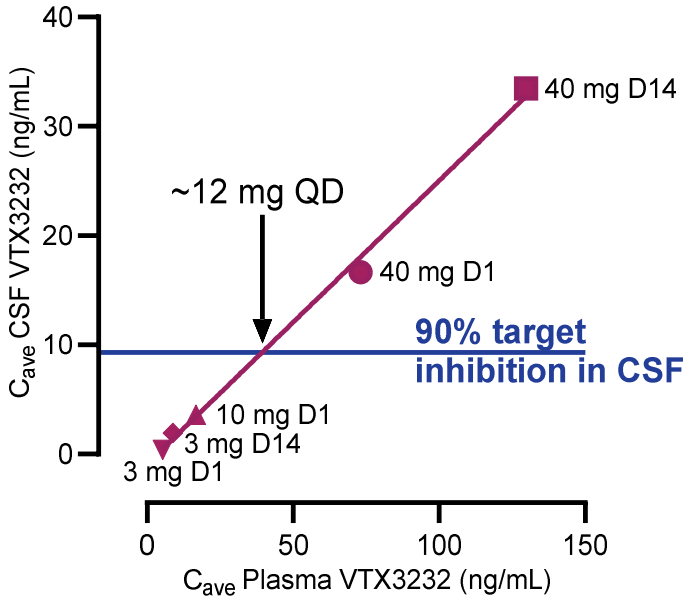
# Conclusions from the Phase 1 Trial of VTX3232 in NHV

## Potentially Class-leading Safety and Efficacy Profile for Neuroinflammatory Diseases

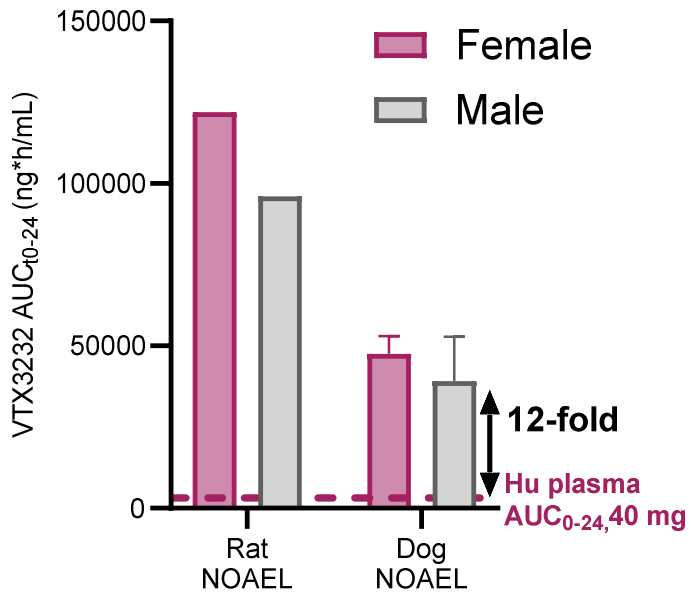
### 40 mg QD Dose: Target Coverage




### Data Predict Low Efficacious Doses




### Toxicology Safety Margin




- **Well-tolerated** in healthy volunteers
- **Robust target coverage achieved in the plasma and CNS**
- **Potent, dose-dependent PD effect** in *ex vivo* IL-1β assay and on inflammatory biomarkers
- **CSF IL-1β $IC_{90}$ coverage for 24h at 40 mg QD**
- **Data predict target coverage ≥ $IC_{90}$ at doses ≥ 12 mg**

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Source: Ventyx internal data.

# VTX3232: Potential First-Mover Position in NLRP3-Mediated Neuroinflammation

## Highly Potent & Selective

- Structurally unique, unrelated to MCC-950
- $K_d$ < 1 nM to NLRP3 NACHT domain
- $IC_{50}$ = 13 nM hu WB, 2.7 nM in microglia
- Selective vs AIM2/NLRC4
- Doses >3 mg suppress IL-1β release for >24 h

## High CNS Target Coverage

- T½ = ~17 h with high free fraction
- High CNS penetration; human Kp,uu = 0.5
- 3 mg QD repeat dosing maintains CSF $IC_{50}$ coverage
- 40 mg QD repeat dosing exceeds CSF $IC_{90}$ coverage

## Promising Safety Profile

- No CYP, hERG, or transporter interactions
- No toxicological signals for further non-clinical study
- Well-tolerated in all SAD/MAD dose groups

## Phase 2 Ready

- IP position secure; patent application published 09/23
- Multi-kilo API production complete
- Solid-oral dosing form with high bioavailability

# NLRP3 Inhibitor Portfolio

## Clinical Development Strategy

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# Building a Diversified Pipeline in Inflammatory Disease

## Broad Potential in Systemic Inflammatory and Neuroinflammatory Conditions

**Ventyx NLRP3 Inhibitors**

### VTX2735

#### Systemic Inflammatory Diseases

- ❖ **Secondary prevention of MACE**
- ❖ **Recurrent pericarditis**
- Metabolic diseases
- Rheumatic diseases
- Dermatologic diseases
- Rare genetic diseases

### VTX3232

#### Neuroinflammatory Diseases

- ❖ **Parkinson's disease**
- ❖ **Obesity**
- Multiple sclerosis (MS)
- Alzheimer's disease
- Amyotrophic lateral sclerosis (ALS)
- Other neurodegenerative diseases

MACE: Major adverse cardiovascular event.

# VTX2735 in Cardiovascular Disease

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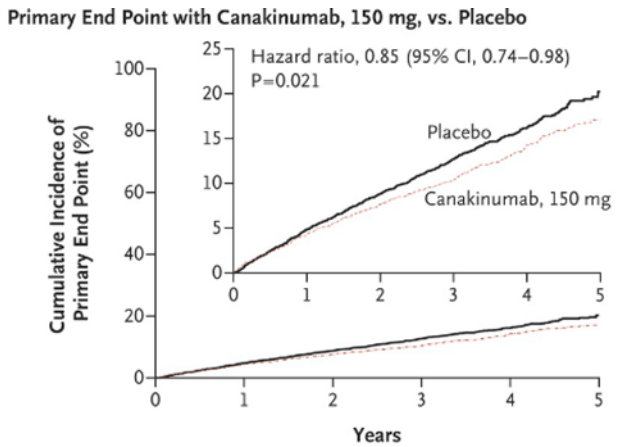
# Attractive Opportunities for VTX2735 in Cardiovascular Disease

## Leading Opportunities – Secondary Prevention of MACE and Recurrent Pericarditis

### MACE Prevention

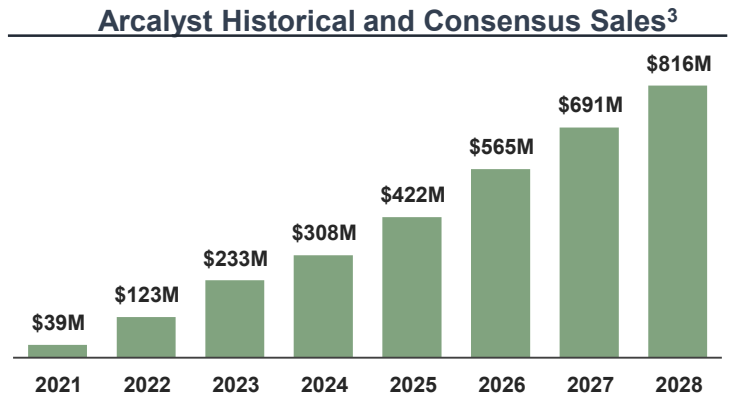
- **CANTOS trial of canakinumab validates IL-1β approach in reduction of MACE risk**
  - Reductions in MACE associated with inflammatory biomarker reductions (hsCRP, IL-6, IL-18)[1]




- **A safe, oral peripheral NLRP3 inhibitor may be an ideal approach for secondary prevention of MACE**
  - Blockbuster opportunity with multiple targetable populations

### Recurrent Pericarditis

- **2021 approval of Arcalyst (rilonacept) validates IL-1α/β approach**
  - ~40,000 patient U.S. prevalent population with RP[2]
  - Arcalyst generated $233M in 2023 sales in 2nd full year of commercial availability; consensus sales **>$800M** in 2028




- **Regulatory precedent for efficient path to market**
  - Open-label Phase 2 followed by a single registrational Phase 3 trial

Source: 1. Ridker et al., *N Engl J Med* 2017; 377:1119-1131 DOI: 10.1056/NEJMoa1707914; 2. Klein et al., *J Am Heart Assoc.* 2021 Aug 3;10(15):e018950. doi: 10.1161/JAHA.120.018950;
3. Historical sales from Kiniksa investor presentation; consensus sales (2024+) from Evaluate Pharma.

# VTX3232 Phase 2a Trial in Parkinson's Disease

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# VTX3232 Has Potential for Disease Modification in Parkinson's Disease

## Strong Mechanistic Rationale and High Unmet Need

### High Unmet Need

- **~1 million** U.S. patient prevalent population (2nd most common neurodegenerative disease)
- **No disease-modifying therapies** approved for Parkinson's disease

### Large Addressable Market

- **>$4B annual market** for symptomatic therapies in 2021[1]
- Estimated **~$10-$15B+ annual TAM** for first disease-modifying therapy[2]

### Strong Biologic Rationale

- **Neuroinflammation** is central to Parkinson's disease pathogenesis
- **Strong evidence** in preclinical models and PD patient samples for NLRP3 as a **key driver** of neuronal degeneration

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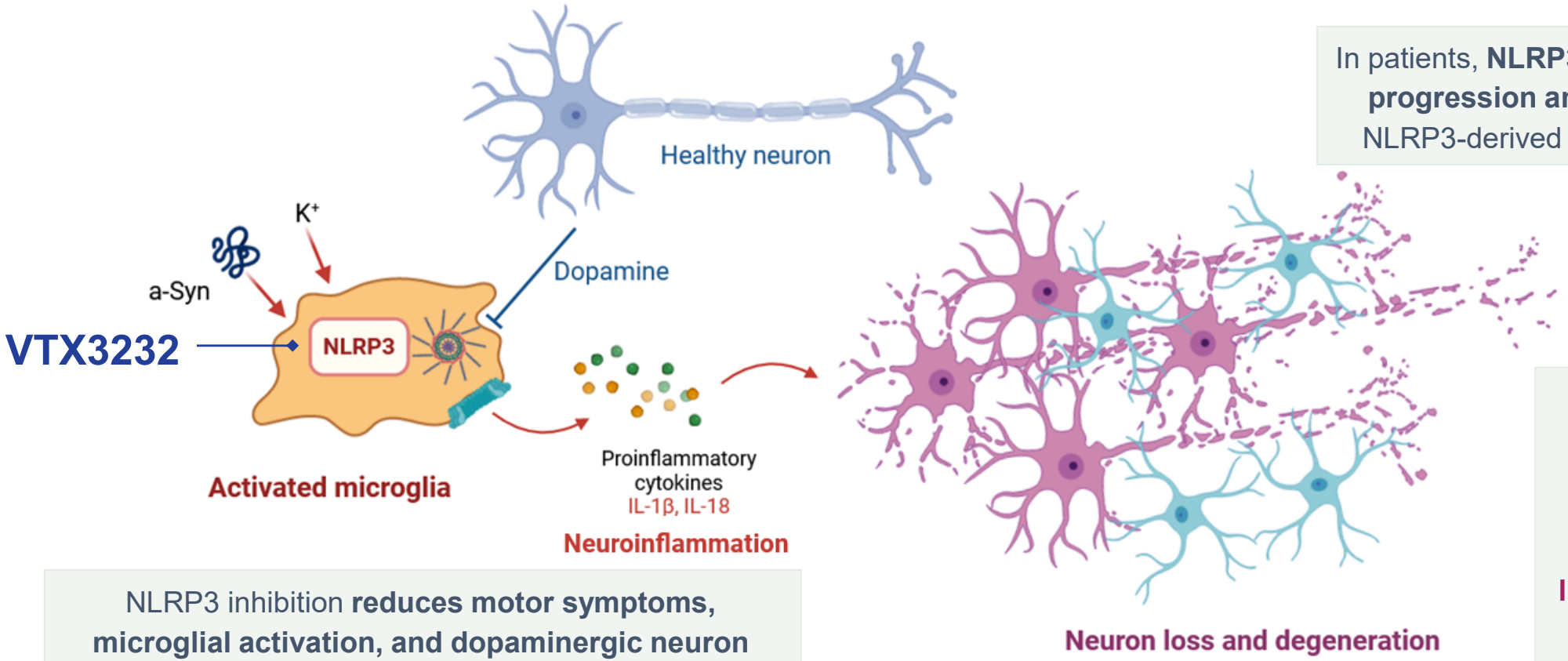
Source: 1. Grand View Research Parkinson's disease market report; 2. ClearView Healthcare Partners market research for internal use.

# NLRP3 Is a Promising Therapeutic Target in Parkinson's Disease

## Neuroinflammation Plays a Central Role in Parkinson's Pathogenesis

There is a growing body of evidence for NLRP3 inhibition as a **potential disease-modifying approach** that may prevent dopaminergic neurodegeneration and clinical symptoms




In patients, **NLRP3 expression is linked to progression and risk of disease**, and NLRP3-derived cytokines are increased

NLRP3 inhibition **reduces motor symptoms, microglial activation, and dopaminergic neuron loss** in multiple distinct animal models of PD

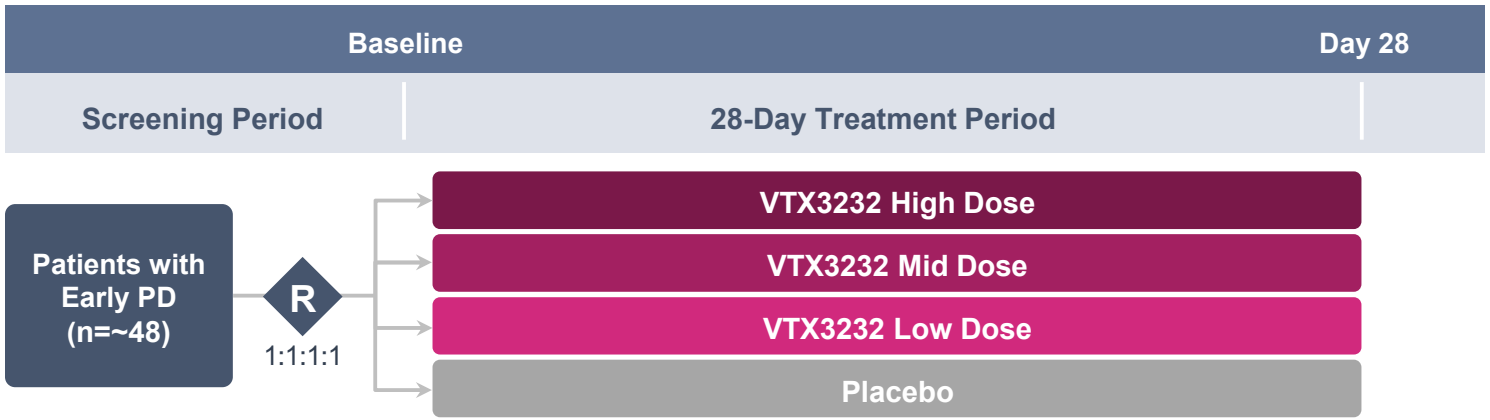
**Neuroinflammation through excess NLRP3 activity may be the mechanistic link driving neuronal cell death in PD**

Source: Liang T et al. 2022 Front. Pharmacol. 13:845185. Ising, C et al. Nature 575, 669–673 (2019). Panicker et al. Neuron. 2022;110(15):2422-2437.e9. Grotemeyer, A. et al., *J Neuroinflammation* 20, 79 (2023). Huang et al., *J Nueroimmunology*, Volume 354, 2021, 577543. Gordon et al., *Sci. Transl. Med.* 10,eaah4066(2018).

# Phase 2a Trial in Participants with Early Parkinson's Disease

## Disease-Relevant Biomarkers and Neuroimaging

- **A Phase 2a trial in participants with early Parkinson's disease is expected to initiate in H2 2024**
  - Impact on relevant plasma and CSF biomarkers: IL-1β, IL-18, α-synuclein, NfL, GFAP, NGAL, Aβ40/42
  - Impact on microglial inflammation via neuroimaging
- **Test of therapeutic hypothesis that CNS NLRP3 inhibition will result in reduced inflammation and disruption of PD pathophysiology**




**Objectives**

- Disease and NLRP3-related biomarkers in plasma and CSF
- Pharmacokinetics
- Neuroimaging for microglial inflammation

Note: preliminary trial design, subject to change pending regulatory feedback.

# VTX3232 Phase 2a Trial in Obesity

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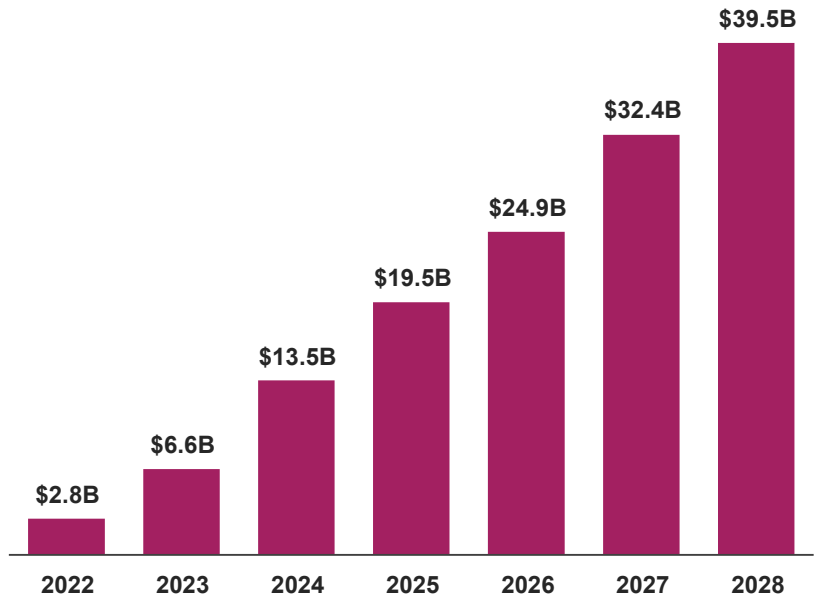
# NLRP3 Is Emerging as an Important Target in Obesity

## The NLRP3 Inflammasome in Obesity and Related Metabolic Disease

- **The NLRP3 inflammasome is emerging as an important axis in obesity and obesity-related metabolic disease**
  - Obesity is a chronic inflammatory condition associated with release of NLRP3-related cytokines such as IL-1β and IL-6
  - This inflammation may drive a range of metabolic disorders, including insulin resistance, diabetes, and atherosclerosis
  - Calorie restriction and exercise-mediated weight loss in obese individuals is associated with reduced expression of NLRP3 and decreased systemic inflammation[1]
- **NLRP3 inhibition drives weight loss in diet-induced obesity (DIO) mouse model[2]**
  - Weight loss effect similar in magnitude to semaglutide (GLP-1)
  - Brain exposure appears necessary for weight-loss effect
  - Inhibition of reactive gliosis (inflammation) in the hypothalamus proposed as potential mechanism

**Projected Growth in the Obesity Market[3]**

*Driven by expected adoption of GLP-1s*




**Blockbuster opportunity for novel mechanisms in obesity and related metabolic impairment**

Source: 1. Vandanmagsar et al., *Nat Med.* 2011 Feb;17(2):179-88. doi: 10.1038/nm.2279; 2. Thornton et al., *Journal of Pharmacology and Experimental Therapeutics* Feb 9, 2024, JPET-AR-2023-002013; DOI: https://doi.org/10.1124/jpet.123.002013 3. EvaluatePharma market projections.

# Phase 2a Trial of VTX3232 in Obese Participants with Elevated CV Risk

## Measuring Key Inflammatory Biomarkers and Changes in Body Composition

- **A randomized, placebo-controlled trial of VTX3232 in obese participants with elevated CV risk is expected to initiate in H2 2024**
  - Adult participants with obesity, elevated CRP, and at least one additional risk factor of atherosclerotic cardiovascular disease
- **Trial intended to efficiently identify a potential efficacy signal and support path forward in obesity**
  - Biomarkers to assess CV risk reduction in obese population; potential to measure other markers of metabolic impairment

**Endpoints**

- Change from baseline in CRP (**primary**)
- Inflammatory biomarkers
- Change from baseline in weight and body composition

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Note: preliminary trial design, subject to change pending regulatory feedback.

# Internally Discovered Clinical-Stage Pipeline

## Addressing Major Autoimmune and Inflammatory Diseases with High Unmet Need

| Target | Program | Preclinical | Phase 1 | Phase 2 | Phase 3 | Next Anticipated Milestones |
|---|---|---|---|---|---|---|
| **NLRP3** *CNS-Penetrant* | VTX3232 | Parkinson's disease, obesity, and other neuroinflammatory diseases | | | | Initiate Ph 2a Parkinson's trial **H2 2024**<br>Initiate Ph 2a Obesity trial **H2 2024** |
| **NLRP3** *Peripheral* | VTX2735 | Cardiovascular and other systemic inflammatory diseases | | | | Phase 2 ready for CV indications |
| **S1P1R** | VTX002 | Ulcerative colitis | | | | Identify partner for Phase 3 trial |
| **TYK2** | VTX958 | Crohn's disease | | | | Phase 2 Crohn's data **mid 2024** |

**Cash, cash equivalents and marketable securities of $252.2M* as of December 31, 2023, are expected to fund operations into at least the second half of 2026**

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* Does not include $100 million gross proceeds raised in PIPE financing announced on March 7, 2024

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