VTX3232: A Novel, Brain-Penetrant NLRP3 Inhibitor for Treating Systemic and Central Inflammation

Bultinck, Jennyfer; Yuan, Shendong; Bracke, Debby; Collins, James; Goethals, Jens; Christianson, Christina; Lloyd, Marit; Gregg, Richard; Ogilvie, Kathleen; Nuss, John; Mohan, Raju

Abstract

NLRP3 plays a role in the fulminant inflammation responsible for the pathology of gouty arthritis, pericarditis and myocardial infarction, as well as the chronic inflammation in many cardiovascular, metabolic and neurodegenerative diseases. We have developed VTX3232 as a potent, selective CNS-penetrant NLRP3 inhibitor active in peripheral (e.g, IC_{50} = 7.1 nM in LPS/ATP-stimulated human monocytes) and central immune cells (e.g., IC_{50} = 2.7 nM in BzATP-stimulated human microglia). VTX3232 has an excellent pre-clinical profile and shows consistently high CNS levels with oral dosing in all species. In pre-clinical work, including diet-induced obesity (DIO) mouse studies, inflammatory markers are consistently lowered peripherally as well as centrally, and in the DIO model, key metabolic parameters are positively affected.

VTX3232 shows a high safety margin in toxicology studies (rat, dog) and is well tolerated in humans. In a Phase 1 clinical trial, single and multiple ascending doses show excellent exposure, target engagement, lowering of inflammatory markers and distribution of the drug to the CNS (human Kp,u,u = 0.50). This evidence supports planned clinical studies in Parkinson's Disease and obese subjects with high hsCRP levels.

VTX3232 Profile

Highly Potent and Selective

- hu WB IC_{50} (IL-1β) = **15 nM**
- hu Microglia IC_{50} (IL-1β) = **2.7 nM**
- Similar efficacy upon a broad range of NLRP3 activators (a.o. nigericin, palmitate, urate crystals, α-synuclein)
- No inhibition of other inflammasomes

Optimal CNS-drug properties in Phase 1

- Excellent 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

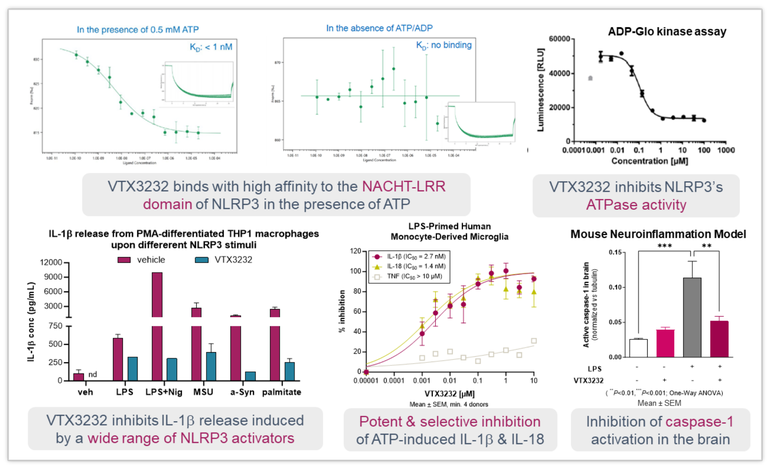
VTX3232 is rationally-designed for **CNS efficacy** without high peripheral exposures

Rapid equilibration across BBB to reach microglial target cells

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

Pharmacological properties

VTX3232 is a Potent NLRP3 Inhibitor



VTX3232 binds with high affinity to the NACHT-LRR domain of NLRP3 in the presence of ATP

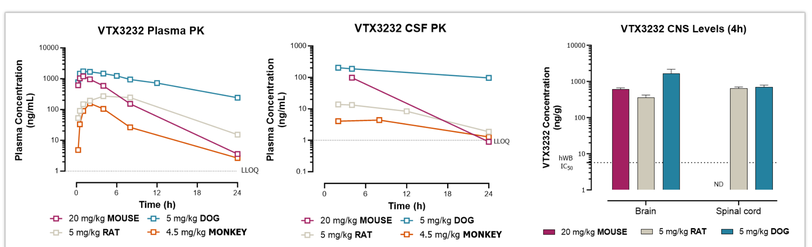
VTX3232 inhibits NLRP3's ATPase activity

VTX3232 inhibits IL-1β release induced by a wide range of NLRP3 activators

Potent & selective inhibition of ATP-induced IL-1β & IL-18

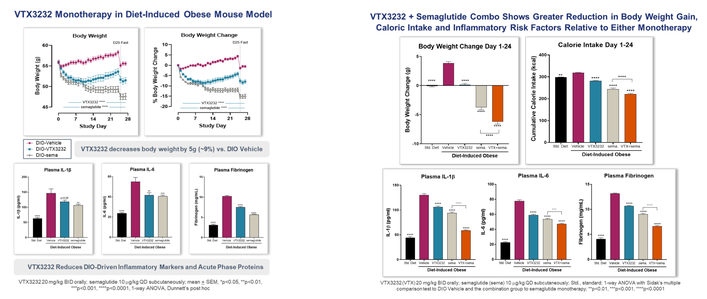
Inhibition of caspase-1 activation in the brain

VTX3232 Has an Excellent PK profile and CNS Exposure



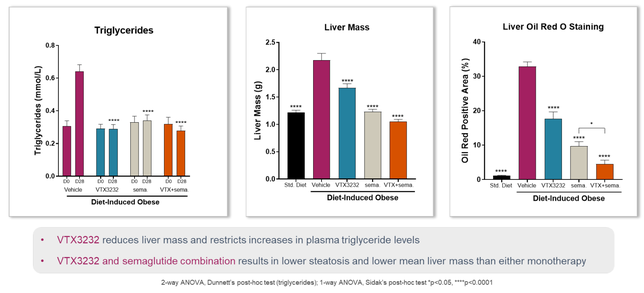
VTX3232 Has Broad Protective Effects In a Mouse Model for Chronic Low-Grade Inflammation Induced by High-Fat Diet.

VTX3232 Limits Body Weight Gain and Reduces Inflammatory Markers and Acute Phase Proteins in Diet-Induced Obese (DIO) mice



VTX3232 (20 mg/kg BID oral); semaglutide (10 μg/kg QD subcutaneously; Std., standard; 1-way ANOVA with Sidak's multiple comparison test to DIO Vehicle and the combination group to semaglutide monotherapy; *p=0.01, ***p=0.001, ****p=0.0001

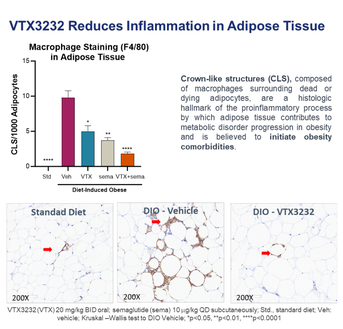
VTX3232 Improves Liver Steatosis



- VTX3232 reduces liver mass and restricts increases in plasma triglyceride levels
- VTX3232 and semaglutide combination results in lower steatosis and lower mean liver mass than either monotherapy

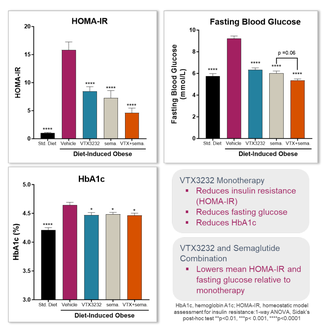
2-way ANOVA, Dunnett's post-hoc test (triglycerides); 1-way ANOVA, Sidak's post-hoc test *p<0.05, ****p<0.0001

VTX3232 Reduces Inflammation in Adipose Tissue



VTX3232 (VTX) 20 mg/kg BID oral; semaglutide (sema) 10 μg/kg QD subcutaneously; Std., standard diet; Veh: vehicle; Kruskal –Wallis test to DIO Vehicle; *p<0.05, **p<0.01, ***p<0.001

VTX3232 Improves Insulin Resistance

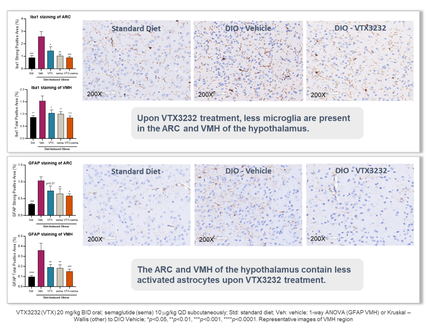


VTX3232 Monotherapy
- Reduces insulin resistance (HOMA-IR)
- Reduces fasting glucose
- Reduces HbA1c

VTX3232 and Semaglutide Combination
- Lowers mean HOMA-IR and fasting glucose relative to monotherapy

HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment for insulin resistance; 1-way ANOVA, Sidak's post-hoc test **p<0.01, ***p< 0.001, ****p<0.0001

VTX3232 Reduces Gliosis in the Hypothalamus

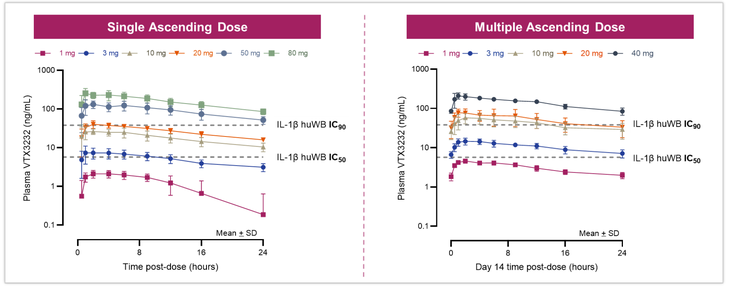


Upon VTX3232 treatment, less microglia are present in the ARC and VMH of the hypothalamus.

The ARC and VMH of the hypothalamus contain less activated astrocytes upon VTX3232 treatment.

VTX3232 (VTX) 20 mg/kg BID oral; semaglutide (sema) 10 μg/kg QD subcutaneously; Std: standard diet; Veh: vehicle; 1-way ANOVA (GFAP VMH) or Kruskal – Wallis (other) to DIO Vehicle; *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. Representative images of VMH region

VTX3232 Phase 1 PK/PD

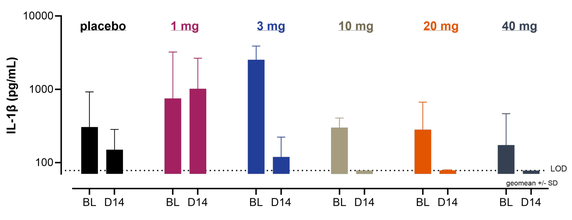


Dose-related, linear exposure from 1 mg to 80 mg

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

VTX3232 Whole Blood Ex Vivo Stimulation Assay

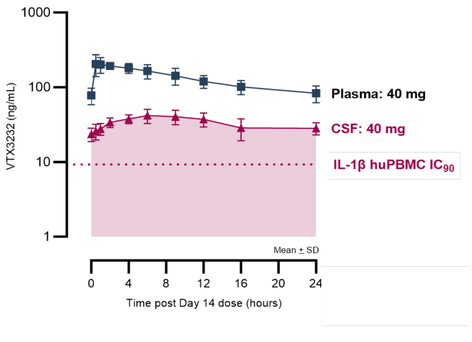
Potent Target Engagement Demonstrated Above 3 mg QD



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

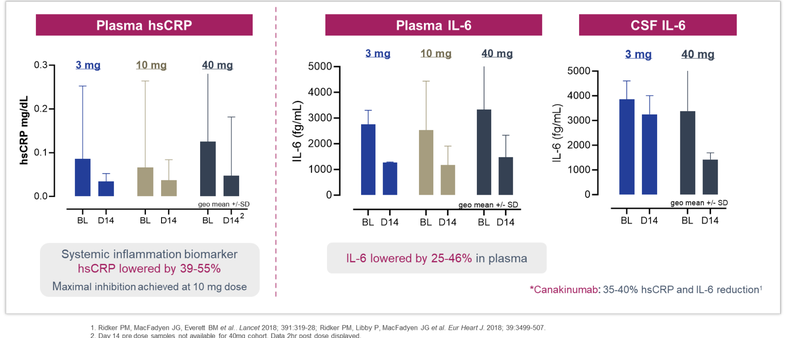
Maximal efficacy achieved at 10 mg dose

40 mg QD Dose: Target Coverage



VTX3232 Effects on Inflammatory Biomarkers

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



Systemic inflammation biomarker hsCRP lowered by 39-55%

Maximal inhibition achieved at 10 mg dose

IL-6 lowered by 25-46% in plasma

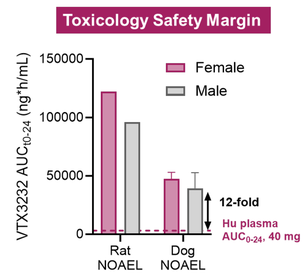
*Canakinumab: 35-40% hsCRP and IL-6 reduction[1]

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.

Safety Assessment

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

Toxicology Safety Margin



Phase II Trials

Phase 2a Trial in Patients with Early Parkinson's Disease:

- approximately ten patients
- 28-day open-label treatment period.
- Primary endpoint: safety and tolerability
- Other outcome measures: pharmacokinetics and relevant biomarkers in plasma and cerebrospinal fluid.
- Topline results expected in 2025

12-week **Phase 2 obesity and cardiometabolic trial** to evaluate the effect of VTX3232 on key inflammatory biomarkers as well as on weight change when dosed as a monotherapy and in combination with a GLP-1 receptor agonist.