VYNE™ THERAPEUTICS

VYN202 P1a SAD/MAD Data

December 2024

ROOTED IN INNOVATION

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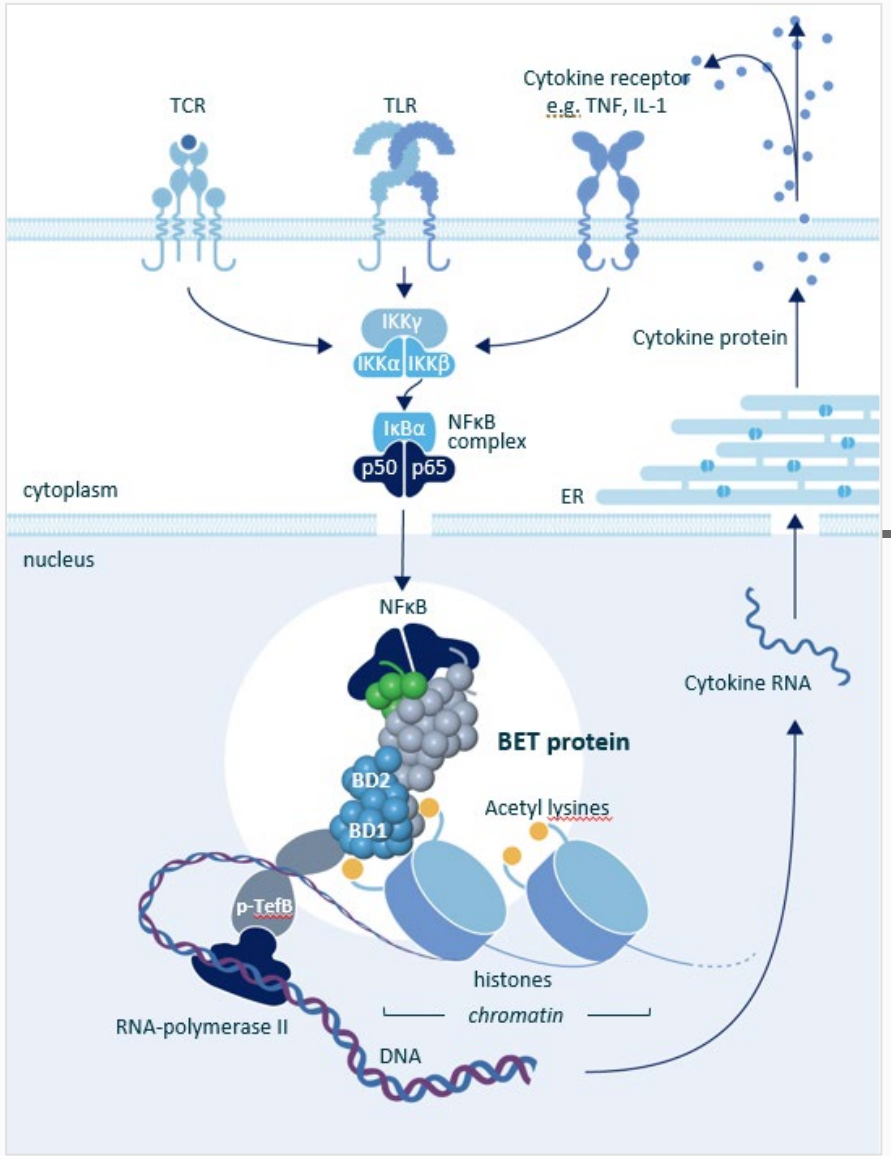
BET Proteins: Key Epigenetic Regulators of NF-kB, a Master Orchestrator of Inflammation



Cell type / Cytokine pathway	Indication
Th1/Tc1 *IL-12, IFNγ, BATF*	**Vitiligo**, Lichen Planus, Alopecia Areata
Th17 *IL-17, IL-23, IL-21, RORC*	**Psoriasis**, PsA, IBD
Tfh *IL-21*	Autoantibody-mediated diseases (e.g., SLE, **RA)**
B cells *BAFF, IL-21, IL-19, IL-22*	Autoantibody-mediated diseases (e.g., SLE, **RA)**
Myeloid cells *TNF, IL-6, IL-1,* *chemokines, adhesion molecules*	**RA**, **psoriasis**, PsA, IBD, Axial SpA, HS

Adapted from Wang, N., Wu, R., Tang, D. *et al.* The BET family in immunity and disease (2021)

VYN202: A Novel BD2-Selective BET Inhibitor for Immune-Mediated Diseases

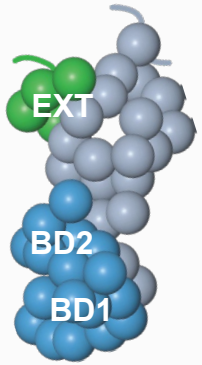
- **VYN202 is an innovative, oral BD2-Selective BET inhibitor**
- **VYN202 is believed to be the most potent and BD2-selective BET Inhibitor in clinical development[1] which is designed to improve efficacy and tolerability**
- **VYN202 has demonstrated a significant inhibitory effect on key disease-related inflammatory biomarkers that correspond with reduced disease severity observed across multiple diverse preclinical models of autoimmune disease**
- **Phase 1 SAD and MAD studies in healthy volunteers complete:**
  - VYN202 was generally well tolerated with no drug-related adverse events historically associated with earlier generation, less selective BET inhibitors
  - Favorable PK profile demonstrated for VYN202, supporting once-daily dosing regimen
  - VYN202 demonstrated robust pharmacodynamic activity including evidence of target engagement and significant inhibition of inflammatory biomarkers relevant to several immune-mediated disorders in ex vivo stimulation assays

Compelling data support VYN202's potential as a novel, once-daily oral treatment for a broad range of immune-mediated disorders

1. Based on readily available public information such as clintrials.gov, academic publications and corporate websites/presentations.

Maximizing On-target Potency vs. BD2 and Minimizing Affinity to BD1 May Be The Key to Optimizing the Benefit/Risk Profile of BET Inhibitors for Autoimmune Diseases

VYN202 is believed to be the most potent and BD2-selective BET Inhibitor in clinical development[1] which is designed to improve efficacy and tolerability



BD2 activity is **associated with inflammatory gene induction** that drives inflammatory responses in autoimmune disease

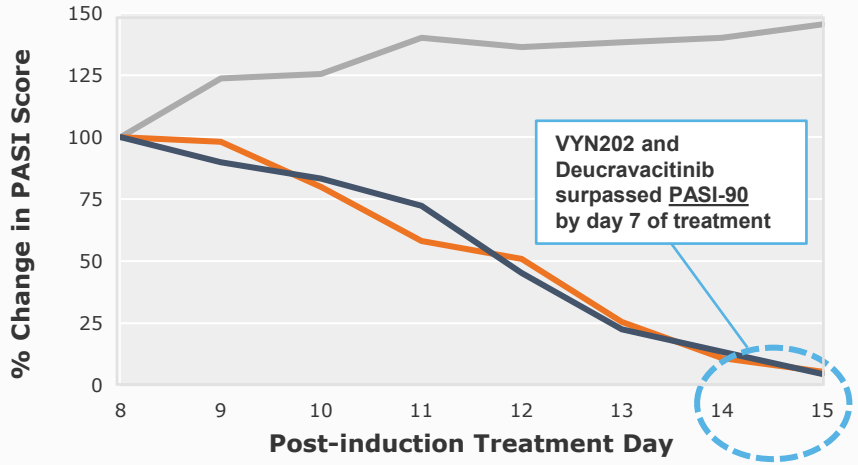
BD1 regulates "housekeeping" gene activity

Compound ID	Potency vs. BD2* (nM)	Selectivity** (BD1/BD2)
VYN202 (VYNE)	**1**	**~10,000**
NUV-868 (Nuvation)[2]	2	1,460x (FRET)
ABBV-744 (AbbVie)[3]	28	753x (FRET)
GSK620 (GSK)[4]	79	220x
Pelabresib (NVS/MOR)[2]	17	5x (FRET)
ABBV-075[3]	13	2.6x
MK-8628/OTX-015[5]	26	1.5x
BI-894999[6]	41	0.1x

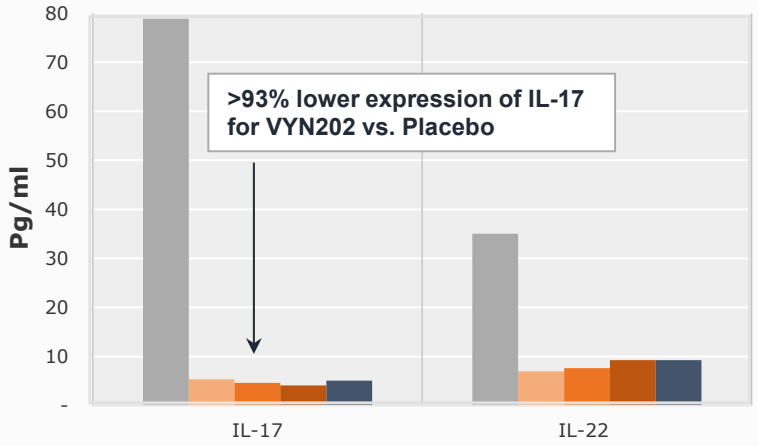
*Lower number denotes higher potency
**Higher number denotes higher selectivity. Data based on nanoBRET assay unless otherwise indicated.

1. Based on readily available public information such as clintrials.gov, academic publications and corporate websites/presentations. 2. Nuvation corporate presentation (August 2024); 3. Faivre et al 2020; 4. Delmont et al 2020; 5. Wang et al 2017 6. Kraut et al 2018; Data on file

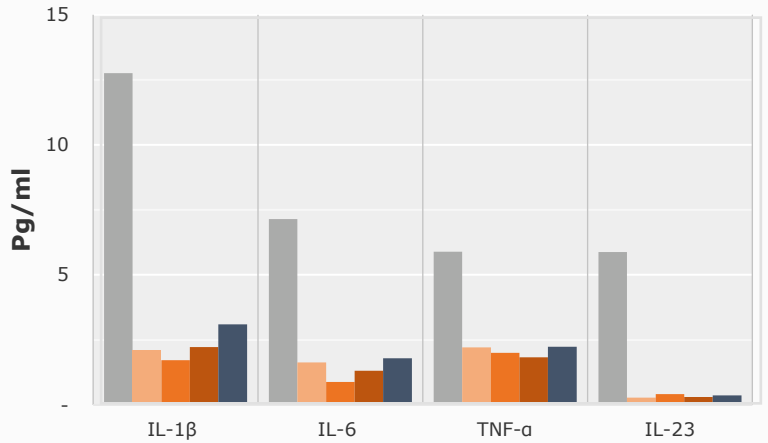
VYN202: Clinical and Biomarker Effects Comparable to Deucravacitinib in Preclinical *in vivo* Model of Psoriasis



Day 15 After 7 days of treatment



>93% lower expression of IL-17 in blood at all VYN202 doses compared to placebo



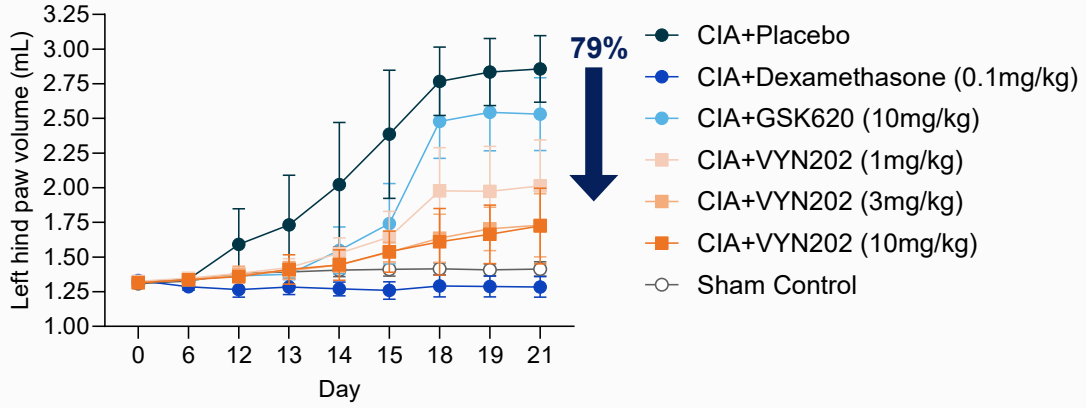
Marked reduction of other disease related Th17 and Th1 cytokines in blood

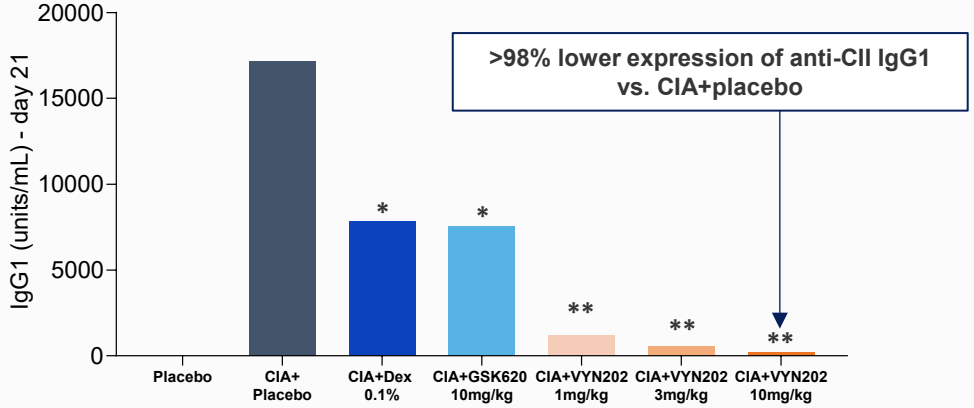
1Sotyktu® (deucravacitinib) was approved in the U.S. in September 2022.; PASI-90 = 90% improvement from baseline in PASI score;
Dorsal depilated BALB-C mice were dosed for 14 days with topical IMI cream (Day 1-7: induction phase, Day 8-14: treatment phase); IMI = imiquimod

VYN202: Anti-Arthritic Effect and Decreased Antibody Levels Demonstrated in Preclinical Models of Arthritis, including a Comparable Effect to Upadacitinib

Collagen-Induced Arthritis Model

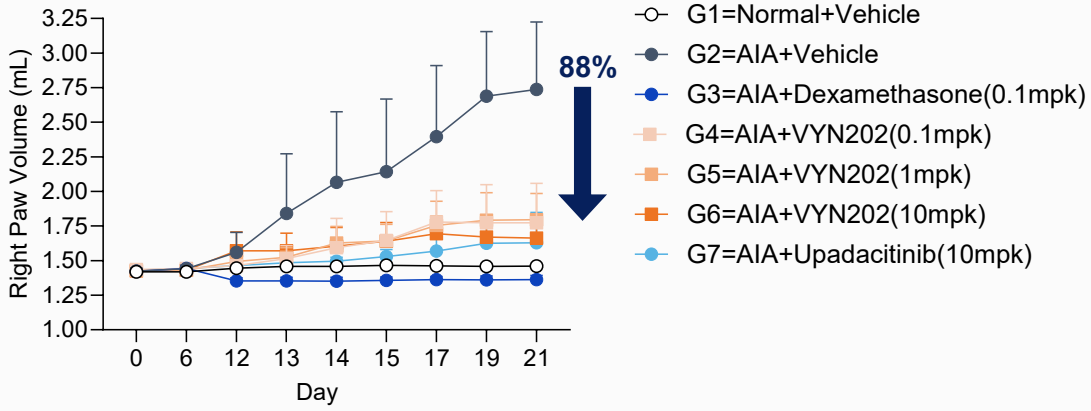
- VYN202's increased potency and selectivity led to improved outcomes vs. early generation BET inhibitor, GSK620
- VYN202 treatment resulted in dose-dependent reduction in severity of histopathology scores; Statistically superior to Placebo and GSK620

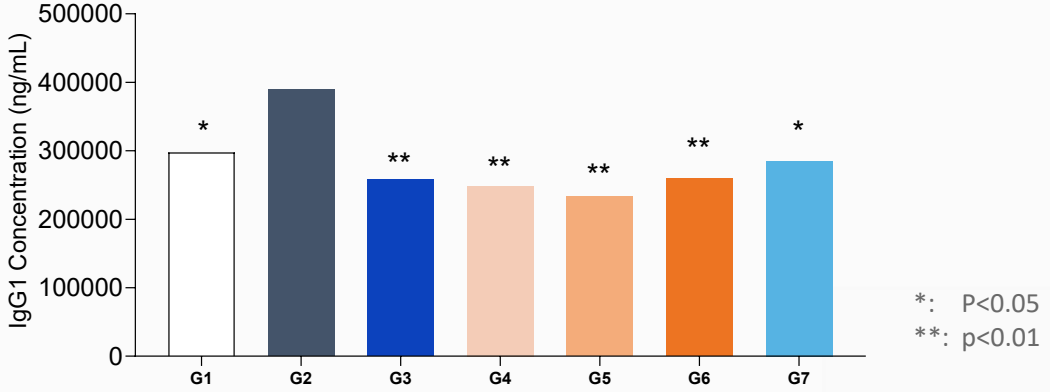




Adjuvant-Induced Arthritis Model

- Comparable effect on paw volume and IgG1 expression to Upadacitinib
- Histopathology scores showed significant effect on preventing ankle inflammation vs. control for VYN202 10mpk (67% reduction vs. control) and Upadacitinib 10mpk (56% reduction vs. control)



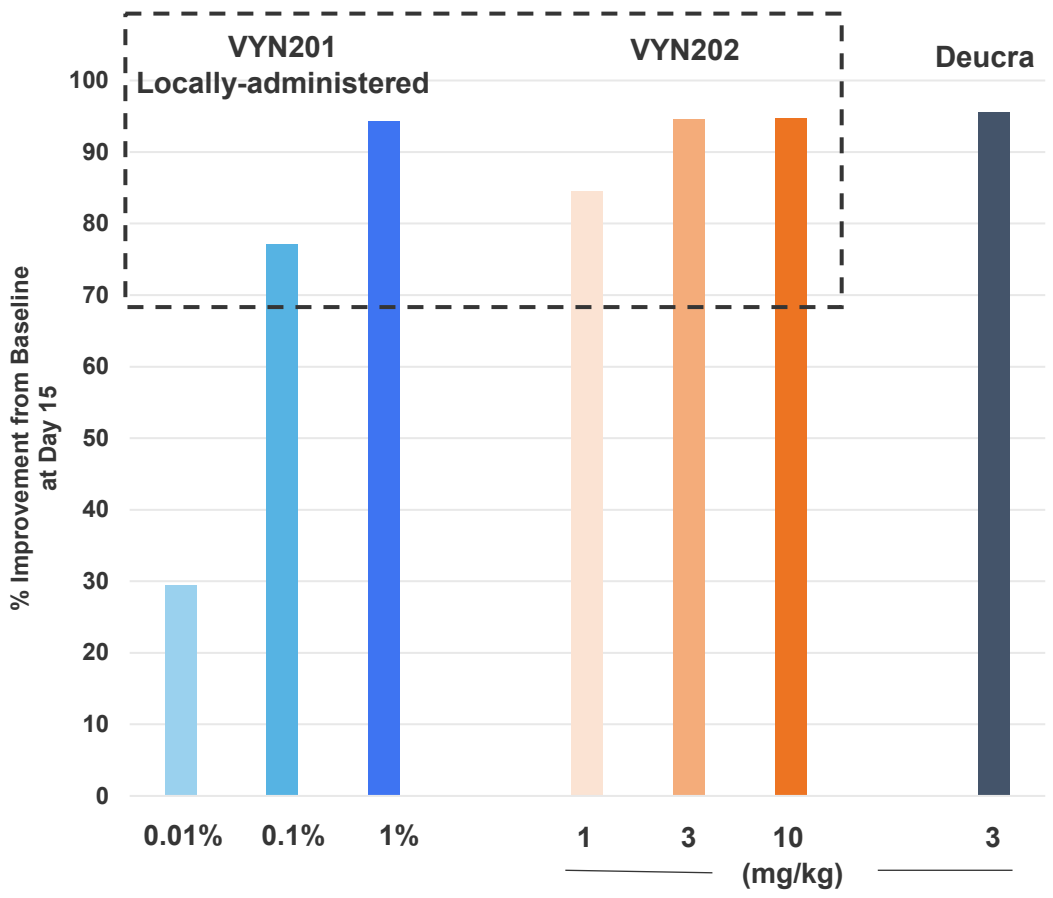


1Histopathology data on file

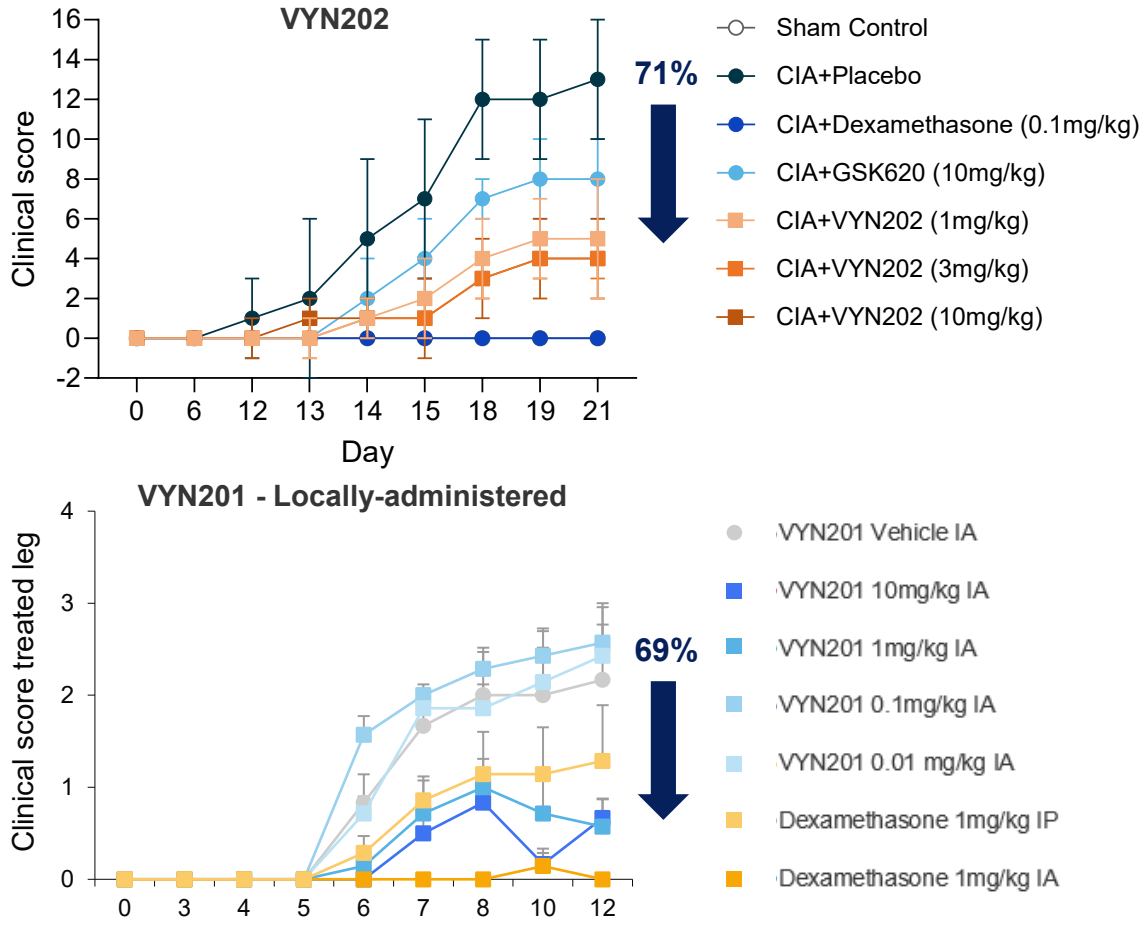
VYN202 Results Show Strong Correlation with VYN201 Results

Reinforcing BET potential and role of BD2 inhibition in treatment of autoimmune diseases

Psoriasis Model



Arthritis Model (CIA)



VYN202: Phase 1a SAD/MAD Data

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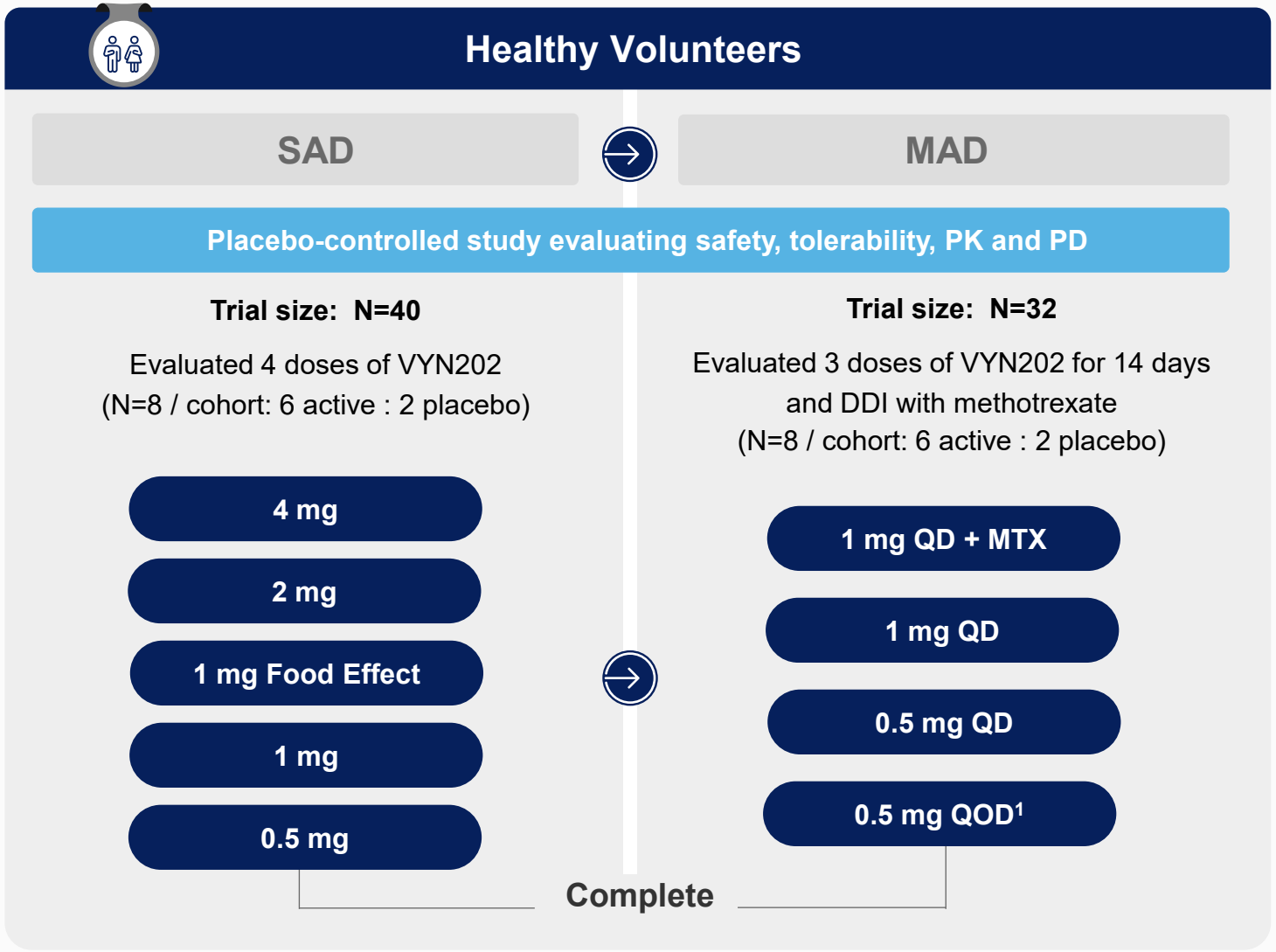
VYN202 Phase 1a SAD/MAD Trial Design and Key Objectives

First-in-human trial in healthy volunteers complete



Key Objectives

Assess:

Safety, Tolerability, Exposure

Exploratory ex vivo pharmacodynamic data:

- Target engagement
- Inflammatory biomarker and cytokine panel

1. Intended to approximate 0.25mg QD dosing; DDI = drug-drug interaction

VYN202 Demonstrated a Favorable Safety and Tolerability Profile in Phase 1

VYN202 was generally well tolerated in Phase 1 MAD with no drug related AEs of special interest historically associated with BET inhibitor class

MAD Results

Treatment Emergent AEs Number of Subjects Reporting (%)	Placebo (n=6)	VYN202		
		0.5 mg QOD (n=6)	**0.5 mg QD** (n=6)	**1 mg QD** (n=6)
Constipation	2 (33.3)			3 (50.0)
Drowsiness	1 (16.7)		1 (16.7)	
Dysmenorrhea	1 (16.7)		1 (16.7)	
Headache	1 (16.7)			1 (16.7)
Pruritus	1 (16.7)		1 (16.7)	

Safety Findings

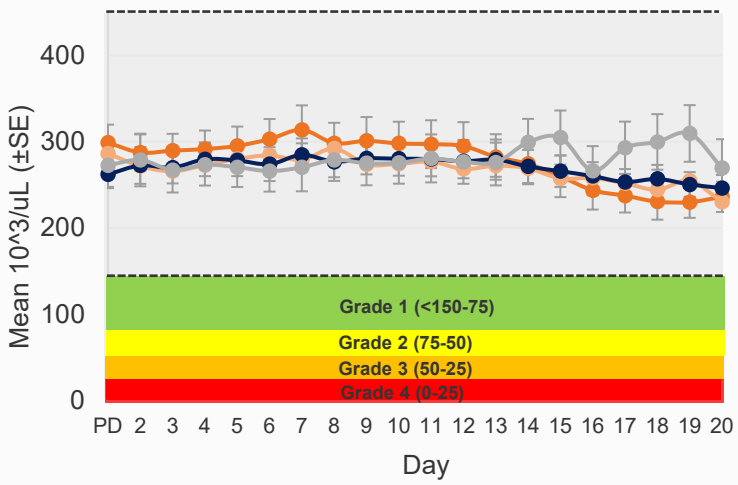
- VYN202 was generally well tolerated
- No serious adverse events or discontinuations due to an AE
- No clinically meaningful treatment emergent AEs
- All treatment emergent AEs considered mild or moderate
- No clinically significant abnormalities in clinical labs or electrocardiogram
- No drug related AEs of special interest historically associated with the BET inhibitor class (thrombocytopenia, neutropenia or gastrointestinal safety findings)

Note: Reported in >1 subject. Excludes those associated with ECG electrode placement and venipuncture reaction

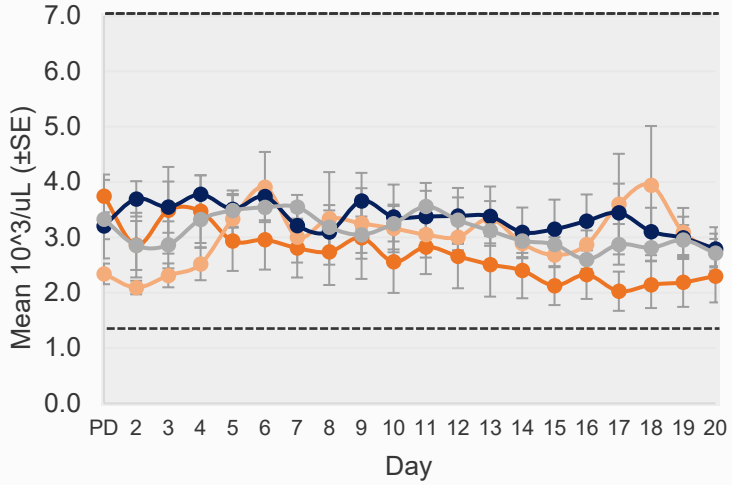
VYN202 Phase 1 MAD Results: Selected Laboratory Data

All laboratory results within normal limits throughout treatment and follow-up period

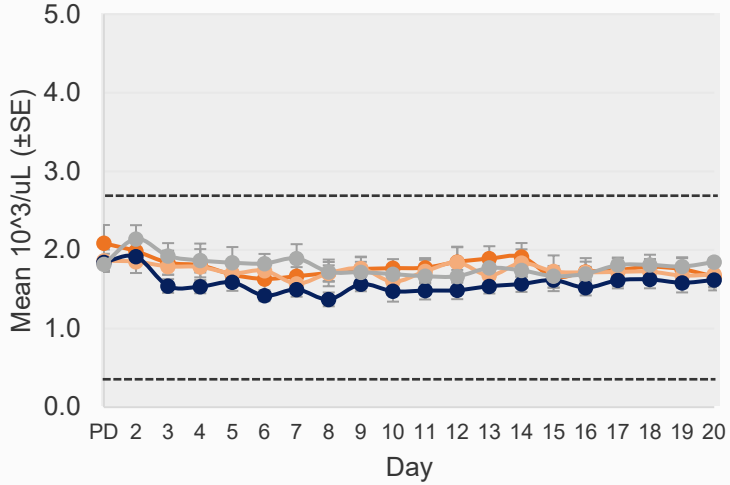
Platelets



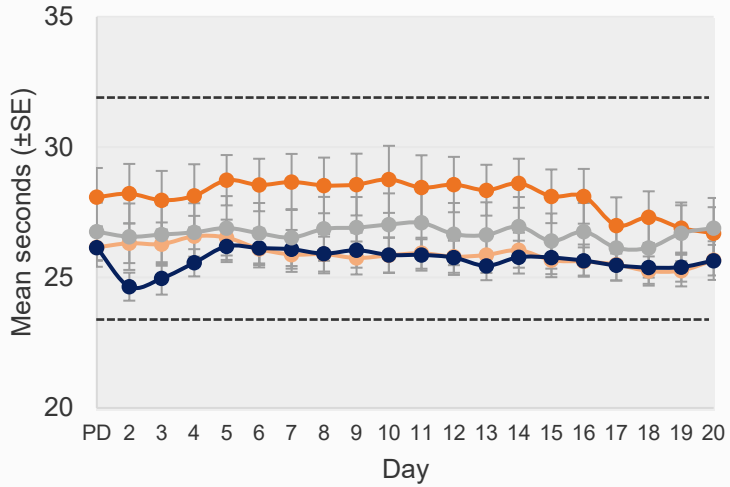
Neutrophils



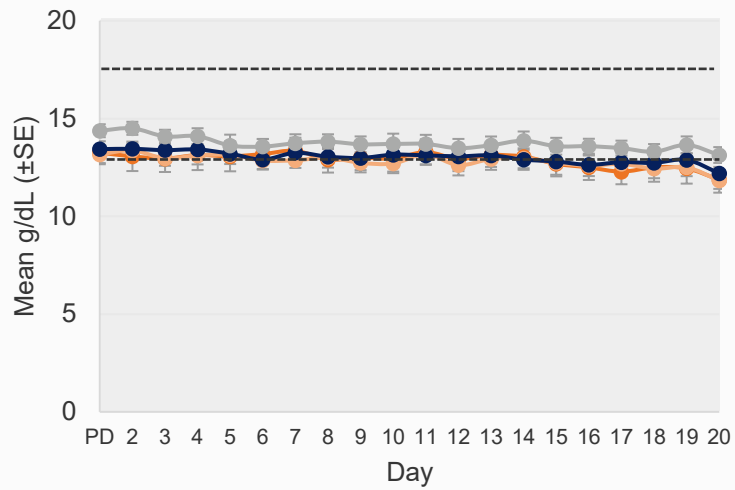
Lymphocytes



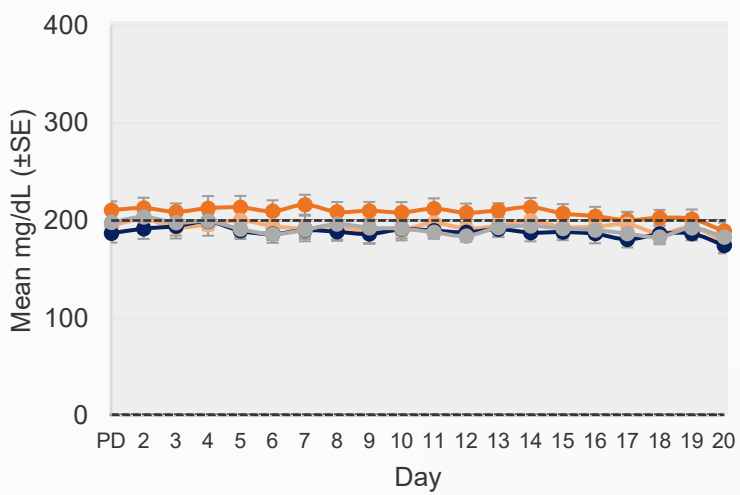
aPTT



Hemoglobin



Cholesterol

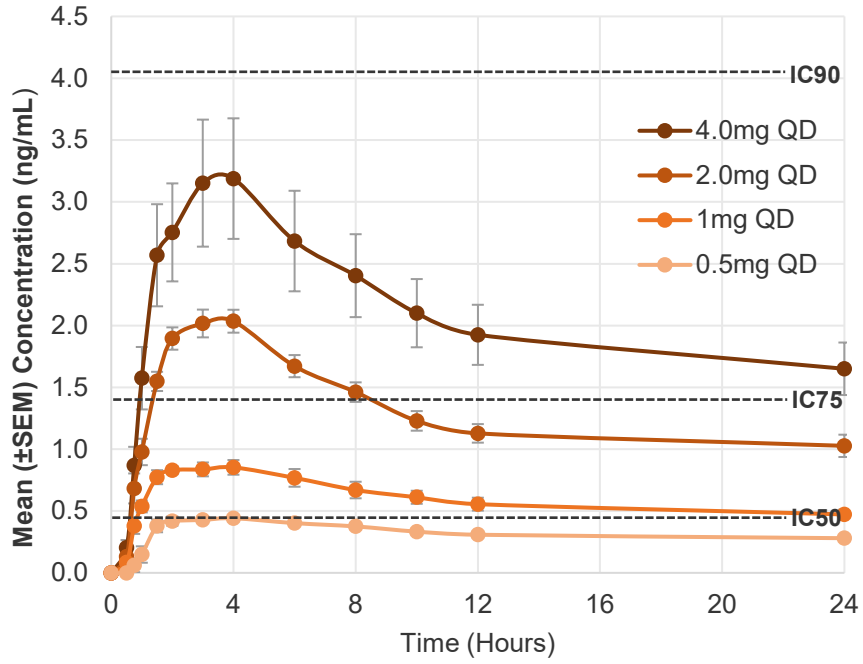


Placebo (n=6) 0.5 mg QOD (n=6) 0.5 mg QD (n=6) 1.0 mg QD (n=6) ----- Upper/Lower limit of normal

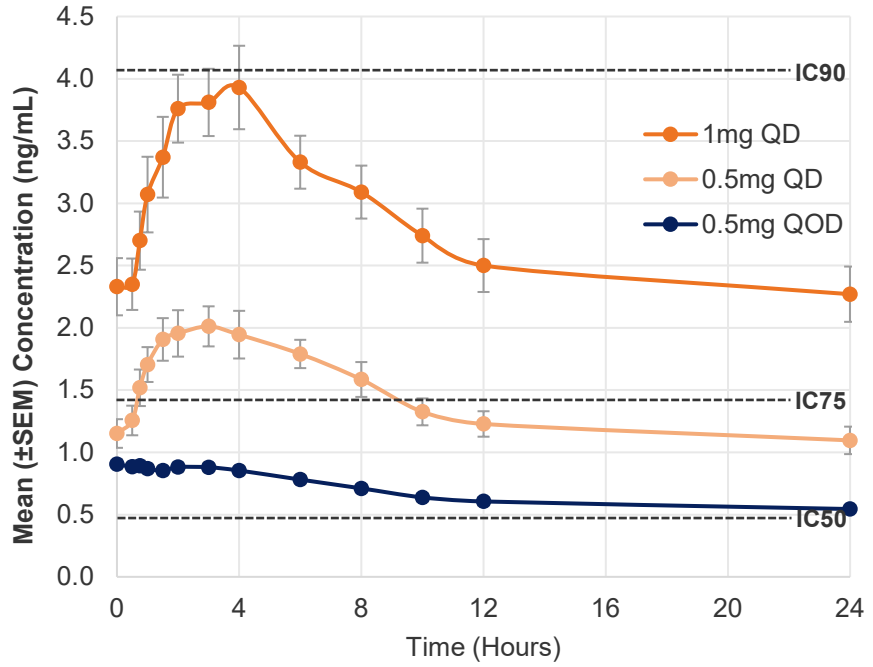
PD=Pre-dose

VYN202 Phase 1 SAD and Day 14 MAD Pharmacokinetics

Single Ascending Dose PK



Multiple Ascending Dose PK, Day 14



- Dose-dependent exposure from dose 0.5 QOD to 4mg, with low variability
- ~4-fold accumulation observed, steady state reached after 7 QD doses
- VYN202 exposure remained above key inhibitory levels vs. BD2 BRD4 for 24 hours post-dose on Day 14
- Median half-life of 36-41 hours supports a once daily dosing posology
- No drug-drug interaction with methotrexate
- Increased exposure with high fat diet

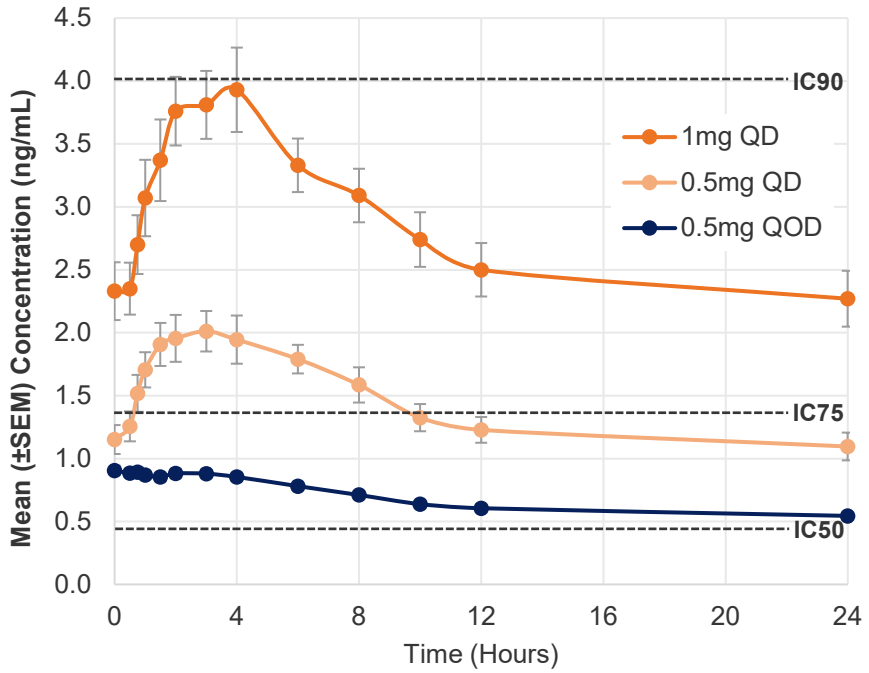
Mean Time Above IC vs. BD2 at Day 14 (hr)		
Dose	IC50	IC75
1 mg QD	>24	>24
0.5 mg QD	>24	~8
0.5 mg QOD	>24	0

IC determined vs. BD2 BRD4 from cell-based nano-BRET assay

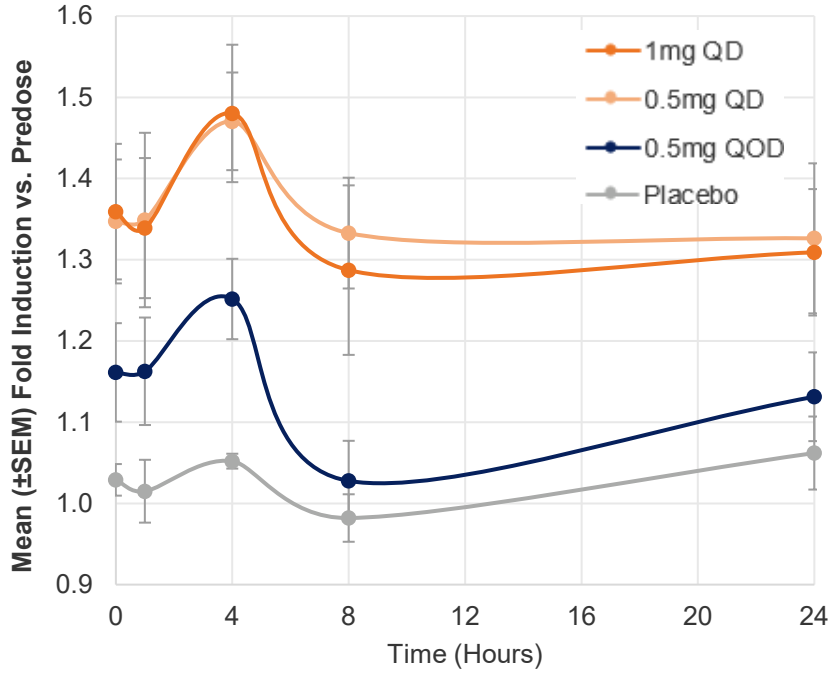
Pharmacokinetics Show Strong Correlation with Target Engagement

Dose-dependent induction of HEXIM-1 with maximum effect observed at 0.5-1.0mg QD

Multiple Ascending Dose PK, Day 14



Multiple Ascending Dose HEXIM-1 Induction, Day 14

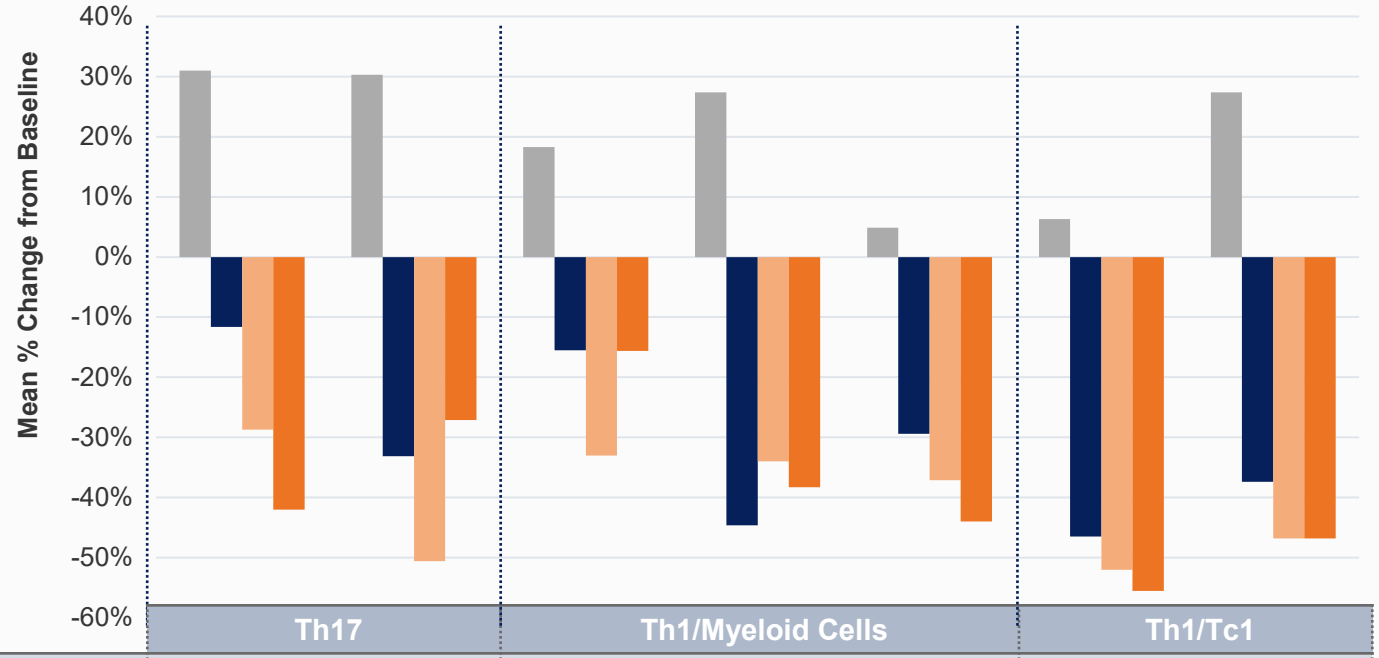


- Inhibition of BET proteins release pTEFb* which activates transcription of pTEFb-dependent genes such as HEXIM-1 leading to higher expression of the HEXIM-1 protein
- Induction of HEXIM-1 closely follows corresponding pharmacokinetics of VYN202 (Tmax: ~4hrs)

pTEFb: positive transcription elongation factor-b

Demonstrated Impact on Pro-Inflammatory and Disease Related Cytokines

Ex Vivo Inhibition of Disease Related Cytokines[1], Day 14



	Th17		Th1/Myeloid Cells			Th1/Tc1	
cytokines	IL-17 (%)	IL-23 (%)	IL-1β (%)	TNF (%)	IL-6 (%)	IFNγ (%)	CXCL10 (%)
Placebo (n=6)	31	30	18	27	5	6	27
0.5mg QOD (n=6)	-12	-33	-16	-45	-29	-47	-37
0.5mg QD (n=6)	-29	-51	-33	-34	-37	-52	-47
1.0mg QD (n=6)	-42	-27	-16	-38	-44	-56	-47
Max Δ vs placebo	-73	-81	-51	-72	-49	-62	-74

Significant inhibition of key cytokines relevant to several autoimmune diseases

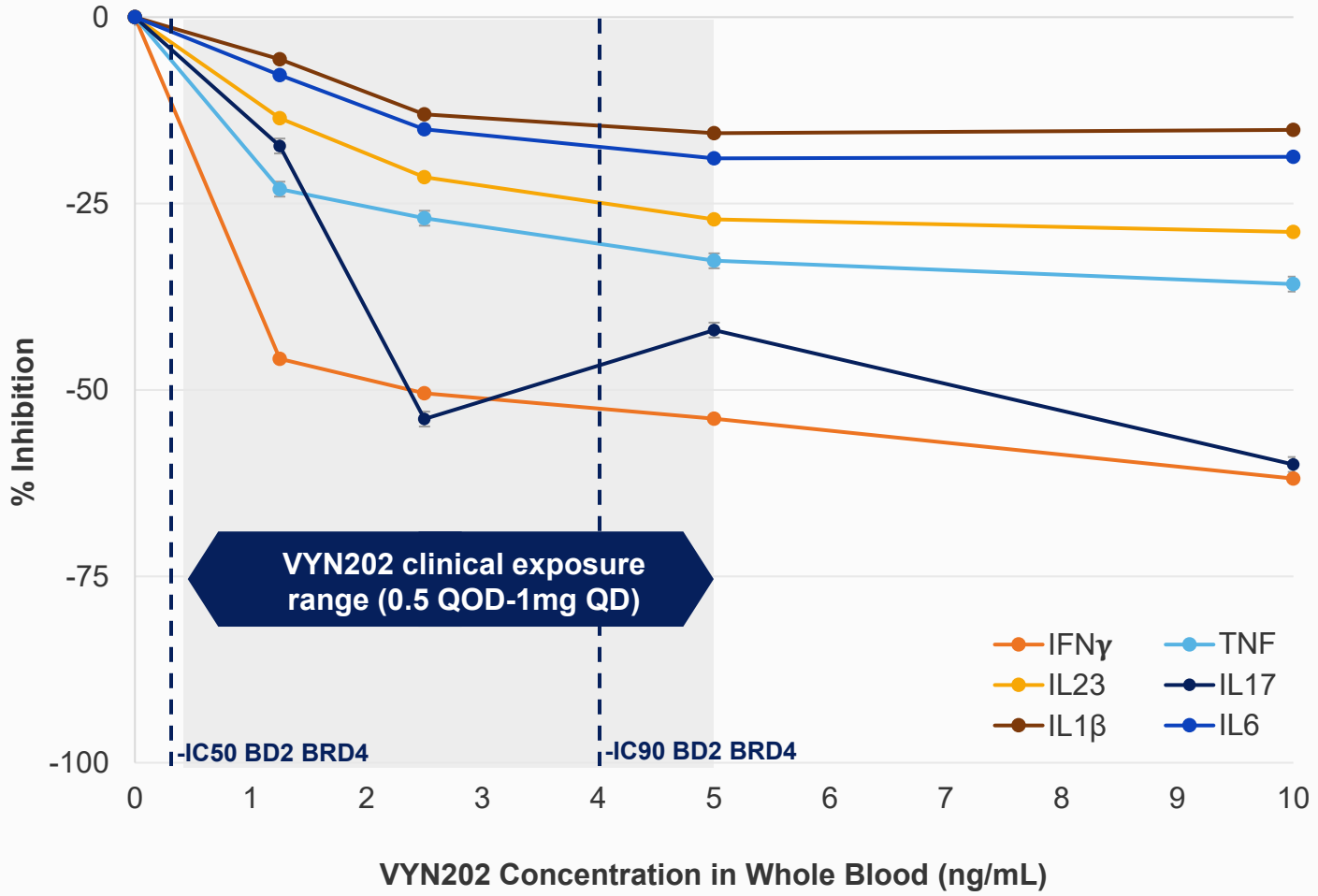
Comparable inhibitory effects to that demonstrated in preclinical efficacy models

Emerging relationship between VYN202 exposure, HEXIM-1 induction and cytokine inhibition

1Using TLR4/TLR7 stimulation and analysis from whole blood samples

Majority of Cytokine Suppression Occurs in Concentrations at 1mg or Below

in preclinical in vitro tests at fixed concentrations of VYN202 ranging from 0 to 10 ng/mL



VYN202 exhibited steep exposure/response curves, consistent with preclinical disease models

Majority of inhibitory effect occurs at exposures equivalent to 0.25mg QD[1] to 1mg QD dosing of VYN202 (0 to 5 ng/mL)

Minimal additional inhibitory benefit with increased exposure beyond 5ng/mL

1. 0.5mg QOD intended to approximate 0.25mg QD dose
2. Mean clinical concentration range of VYN202 is approximately 0.5 ng/mL (0.5mg QOD trough concentration at steady state) to approximately 5 ng/mL (1mg Cmax at steady state).

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VYN202 Phase 1a MAD Data Summary

Safety

- Demonstrated favorable safety and tolerability profile
- No drug-related adverse events historically associated with earlier generation, less selective BET inhibitors, including thrombocytopenia, neutropenia or gastrointestinal toxicity findings
- No serious adverse events (AEs), discontinuations due to an AE or clinically meaningful treatment emergent adverse events (TEAEs)
- All TEAEs were considered mild or moderate in severity
- No drug-related adverse events associated with laboratory results
- There were no AEs of any severity grade relating to thrombocytopenia, which is a known dose-limiting toxicity associated with earlier generations of BET inhibitors

Pharmacokinetics

- Favorable PK profile
- Data supports once-daily dosing regimen
- VYN202 demonstrated dose dependent exposure that reached steady-state after 7 once-daily doses
- VYN202 blood levels were within key inhibitory thresholds of IC50 to IC90 against BD2 BRD4 for at least 24 hours at all doses
- No drug-drug interaction observed when VYN202 was co-administered with methotrexate, a treatment commonly used in the management of chronic immuno-inflammatory conditions

Pharmacodynamics

- Robust pharmacodynamic activity on target engagement and inflammatory biomarkers in ex vivo assays
- VYN202 induced a dose-dependent increase in the target engagement biomarker HEXIM-1 with a maximal effect observed at 0.5mg to 1.0 mg QD
- VYN202 inhibited the production of multiple inflammatory biomarkers related to Th17, Th1/myeloid and Th1/Tc dysregulated activity, consistent with preclinical models of VYN202
- VYN202 exhibited steep exposure/response curves, consistent with preclinical disease models, with majority of inhibitory effect occurring at exposures equivalent to 0.25mg QD to 1mg QD dosing of VYN202 (0 to 5 ng/mL)

Compelling data support VYN202's potential as a novel, once-daily oral treatment for a broad range of immune-mediated disorders