VYNE™ THERAPEUTICS

Corporate Presentation

November 2023

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Investment Highlights (NASDAQ: VYNE)

Advancing novel BET inhibitor platform to improve the lives of patients suffering from immuno-inflammatory conditions

Innovative Target & Approach

- BET inhibition represents a novel target for the treatment of autoimmune diseases: Addressing the complex signaling of immuno-inflammatory diseases by disrupting inflammatory gene transcription in T cells
- Potential across broad range of immune-mediated diseases representing multi-billion-dollar opportunities

Clinical Stage Pipeline

- VYN201: Phase 1b PoC data in vitiligo suggest VYN201 has the potential to be category leader
- VYN202: Supported by robust preclinical data across multiple diverse models of autoimmune disease, Phase 1a SAD/MAD expected to be initiated in Q1 2024 following IND clearance

Potential for Multiple Clinical Catalysts

- VYN201: Phase 2b trial expected to be initiated in 1H 2024 targeting top-line results in mid-2025
- VYN202: Phase 1a SAD/MAD read-out anticipated mid-2024
  - (2) Phase 1b PoC studies in plaque psoriasis and rheumatoid arthritis planned with targeted top-line results expected in mid-2025

Experienced Team & Strong Balance Sheet

- Seasoned leadership team with demonstrated track record of progressing programs through regulatory approval
- Pro forma cash: $103.7M[1]; No debt
  Recent financing with syndicate of leading healthcare investors provides cash runway through the end of 2025

1. As of September 30, 2023, reflecting gross proceeds from $88 million PIPE financing in October 2023; Pro forma shares outstanding: ~14.0M; Pro forma fully-diluted shares outstanding: ~42.8M excluding treasury stock method; unaudited

Building a Leading Early-Stage Pipeline to Address Unmet Needs in I&I Conditions

Program	Indication(s)	Route of Administration	Current Stage				Status / Next Anticipated Milestones	Rights
			Preclinical	IND-Enabling	Phase 1	Phase 2		
InhiBET™ Platform - Library of NCE BET Inhibitors for Any Indication Worldwide								
VYN201 Soft pan-BD BET inhibitor	Nonsegmental Vitiligo	Topical			→		• Phase 1 completed • 1H 2024: Initiate P2b	Worldwide
VYN202 BD2-selective BET inhibitor	Moderate-to-Severe Plaque Psoriasis	Oral		→			• IND-enabling studies ongoing • Q1 2024: Initiate P1 SAD/MAD	Worldwide
	Moderate-to-Severe Rheumatoid Arthritis			→				
Ongoing evaluation for other autoimmune and fibro-inflammatory diseases								

Based on current estimates.

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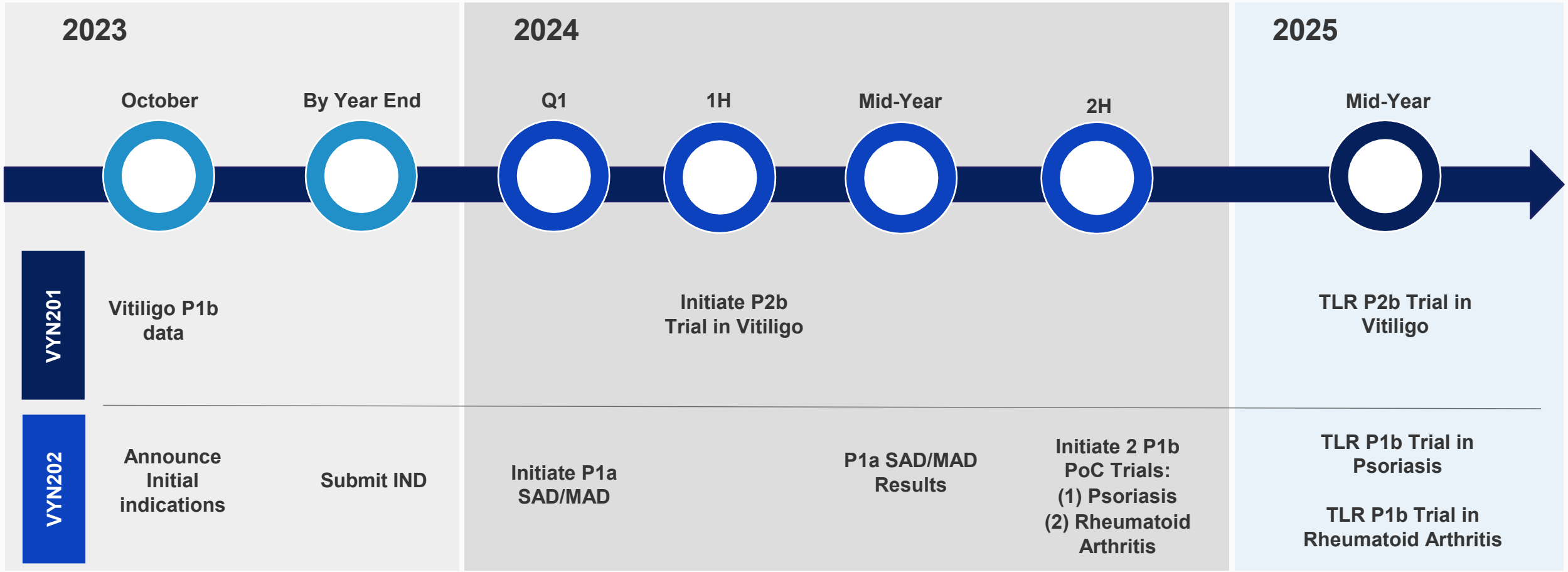
Multiple Paths to Potential Value Creation Across BET Inhibitor Programs



Cash runway through the end of 2025

Based on current estimates.

InhiBET™ BET Inhibitor Platform

Bromodomain & Extra-Terminal Domain (BET) Inhibition for Immunology and Inflammatory Diseases

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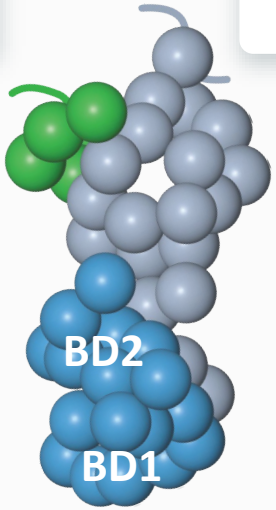
VYNE's Drug Design Strategy

Optimize benefit/risk profile of BET inhibitors to target autoimmune diseases

VYN201
Pan-BD BET Inhibitor

Maximize local effect & minimize systemic exposure

- Tissue targeted administration routes & formulations
- Soft drug / drug delivery strategies to reduce impact of BD1 inhibition on steady-state gene regulation



VYN202
BD2-Selective BET Inhibitor

Improve efficacy and tolerability through BD2-selectivity

- Class-leading BD2 vs. BD1 selectivity for systemic administration
- BD2 activity more relevant to inflammatory gene expression
- Minimize BD1 inhibition to protect against steady-state gene disruption

Gilan et al, Science. 2020 April 24; 368(6489): 387–394

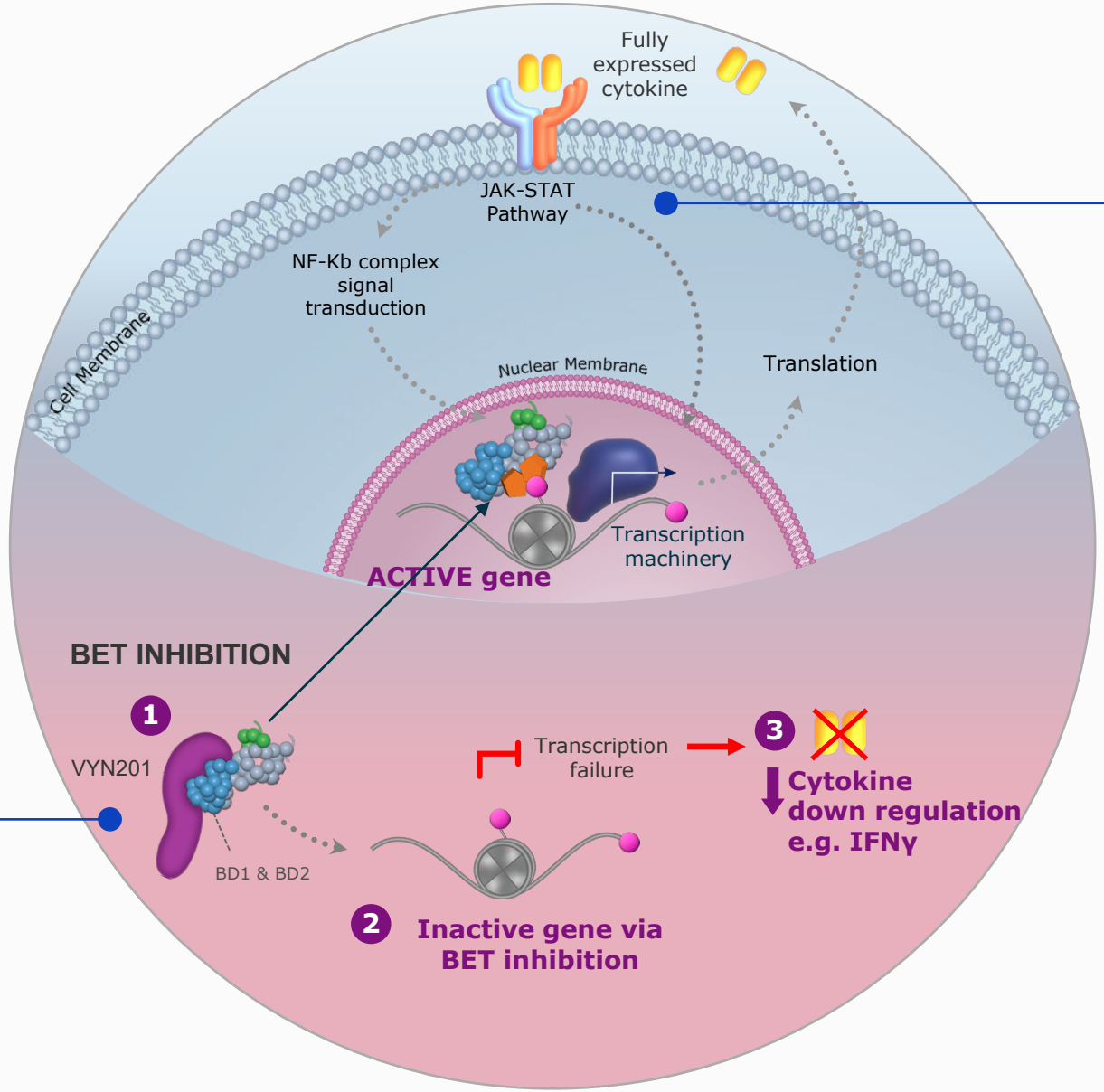
Dawson et al, Science 2020; Belkina, Nikolajczyk & Denis, J. Immunol. 2013

VYN201: Vitiligo

BET Inhibition – A Differentiated Treatment Strategy for Non-Segmental Vitiligo

BET Inhibition (VYN201)

- BET proteins recognize (“read”) acetylated lysine on the termini of histones that protrude from chromatin.
- **BET inhibition prevents transcriptional processing, leading to signal transduction termination.**



JAK-STAT pathway Opzelura® (ruxolitinib)

- JAK activation phosphorylates receptors that form docking sites for STAT
- **JAK inhibition prevents STAT signal transduction into the nucleus.**

Adapted from Gonzalez-Gay et al, Autoimmunity Rev, (2020) 19: 102429 and Rusinol and Puig, Int J Mol Sci, (2023) 24: 3391

Vitiligo – Significant Unmet Need

Only one drug currently approved; treatment is dominated by non-specific therapeutics

Current Treatment Paradigm

1L

- Topicals (Corticosteroids, topical calcineurin inhibitors, ruxolitinib)
- Phototherapy
- Excimer Laser

2L

- Phototherapy + Topicals
- Systemic steroids

3L+

- Surgery (skin tissue grafting; hair follicle transplant)

Opportunity

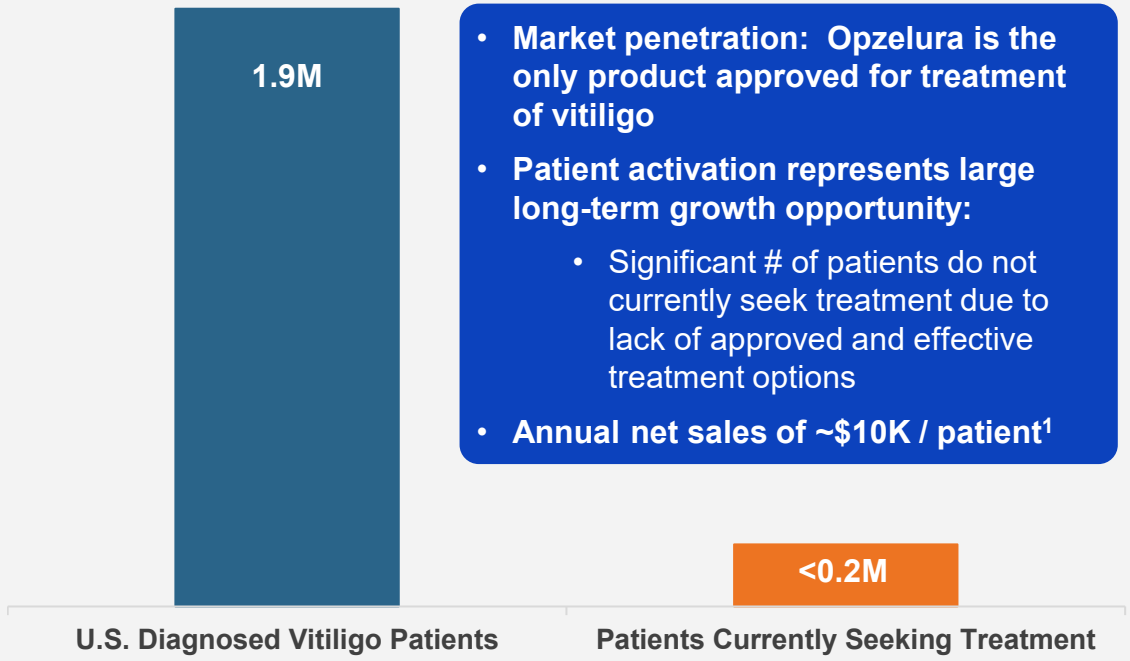
- **Large unsatisfied market**
  - Significant # of patients do not currently seek treatment due to lack of approved and effective treatment options
  - Time to optimal repigmentation 6-24 months
- **Current treatments dominated by non-specific therapeutics that are burdensome to patients**
  - Only one drug approved Opzelura® (ruxolitinib) with black-box warning
  - Limited clinical development activity (almost exclusively JAKs)
  - Modest efficacy and safety challenges of available treatments = market can support multiple new product entries

- **Treatment algorithms suggest topicals utilized at all stages including concomitant use**
- **Targeted, safe, faster treatment options needed that could lower disease recurrence rates**

Source: UptoDate; Bergqvist. Dermatol. 2020;236:571-592; Karagaiah. Expert Opin Emerg Drugs. 2020;25(1):7-24

Vitiligo Represents a Large and Growing Market Opportunity

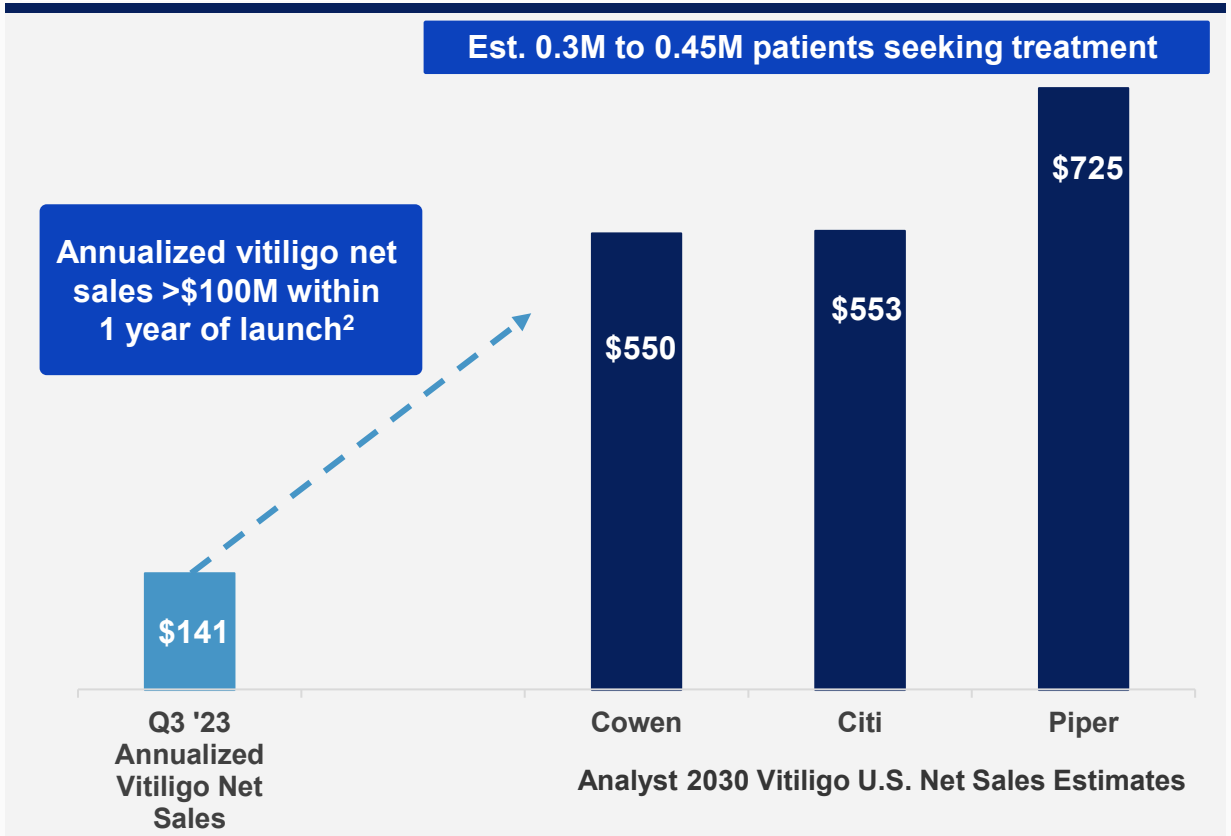
Addressable Market



- **Market penetration: Opzelura is the only product approved for treatment of vitiligo**
- **Patient activation represents large long-term growth opportunity:**
  - Significant # of patients do not currently seek treatment due to lack of approved and effective treatment options
- **Annual net sales of ~$10K / patient[1]**

Opzelura® (ruxolitinib) cream 1.5%

$ in millions



2022 acquisition of Villaris for preclinical vitiligo asset auremolimab underscores attractive opportunity for VYN201 ($70M upfront / $1.4B total deal value)

Source: Gandhi et al. JAMA Dermatol. 2022;158(1):43-50; Kruger. 2012;51(10):1206-1212; Rangu. J Clin Dermatol Ther. 2021;7:070; Pandya. AAD 2023 Presentation; Incyte Corporate Pres. Aug. 2023; TD Cowen research dated Sept. 2023; Piper research dated Jan. 2023; Citi research dated July 2023

1. Opzelura pricing: $2k per 60g tube*10 tubes per patient per year less GTN discount of 50% per Incyte mgmt.; 2. Estimated: Q3'23 net sales $88mm with vitiligo representing ~40% of TRx per Incyte mgmt.

VYN201: Preclinical Data

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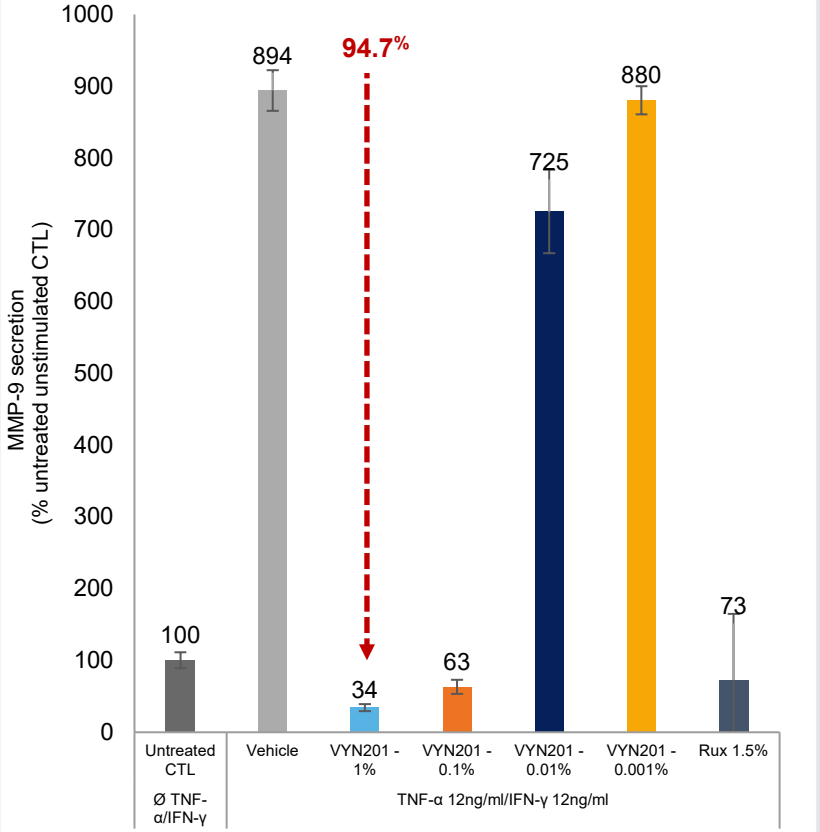
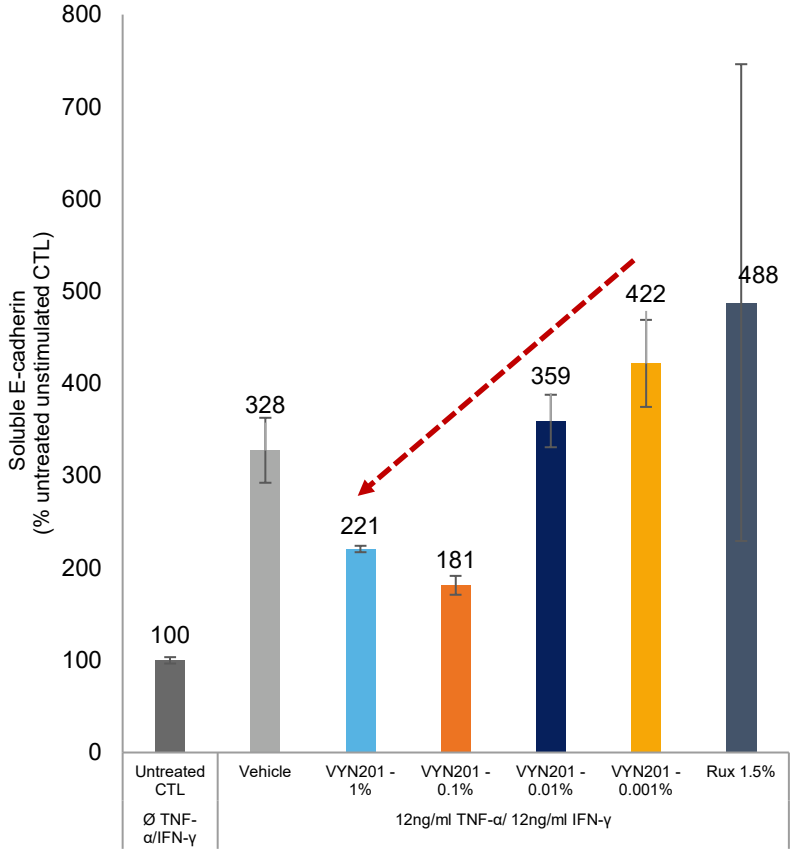
VYN201: Human Tissue Model of Vitiligo

Demonstrated reduction in melanocyte loss and lowering of key inflammatory biomarkers

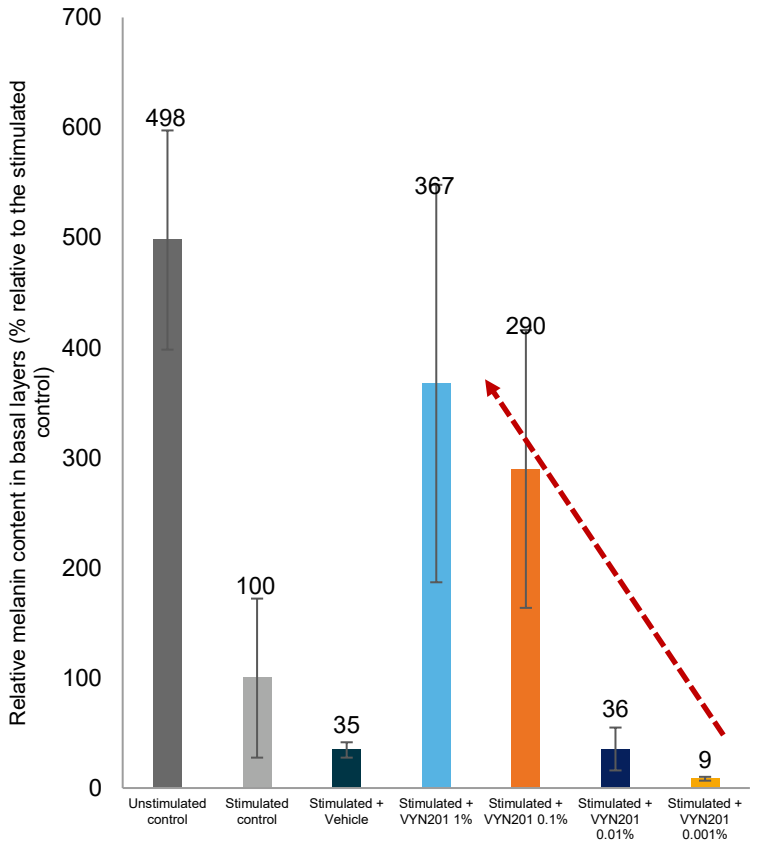
VYN201 1% **reduced the secretion of MMP9** relative to stimulated vehicle, and numerically superior to ruxolitinib 1.5%



VYN201 affects a **dose-dependent reduction in solubilized E-cadherin**



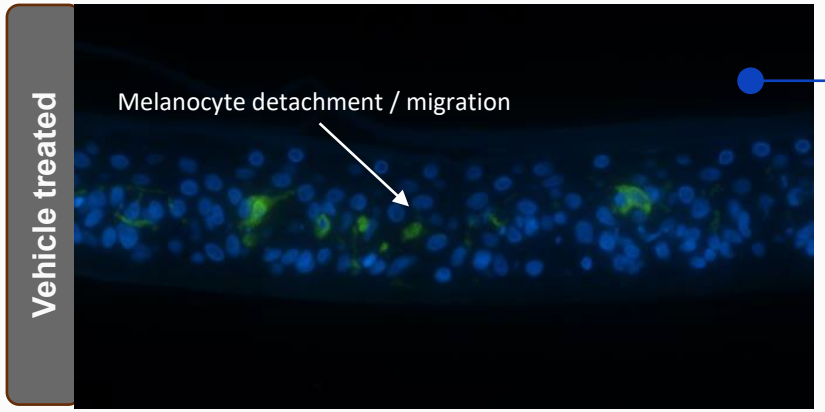
VYN201 **substantially prevents the loss of melanin** pigment in the basal layers of skin in a dose dependent manner



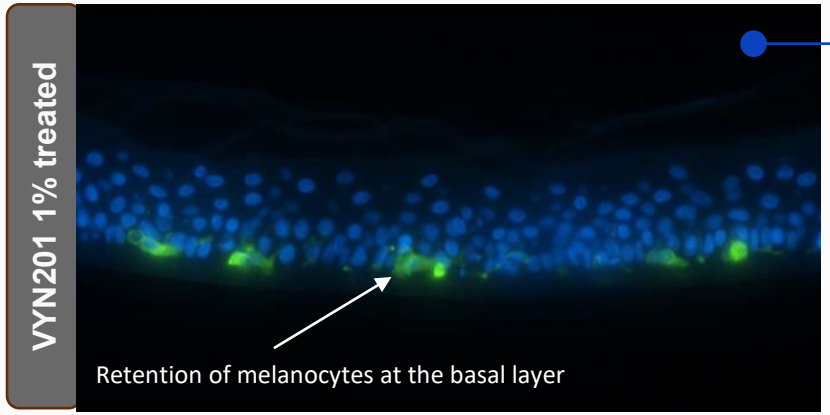
Reconstituted human epithelial (RHE) skin cultures were treated with a TNF-α and IFN-ɣ cytokine cocktail to induce a vitiligo phenotype melanocytorrhagy (loss of melanocyte), upregulation of MMP9 and soluble E-cadherin).

VYN201: Human Tissue Model of Vitiligo

VYN201 prevents melanocyte detachment, down regulates the expression of key cytokines and upregulates WNT pathway



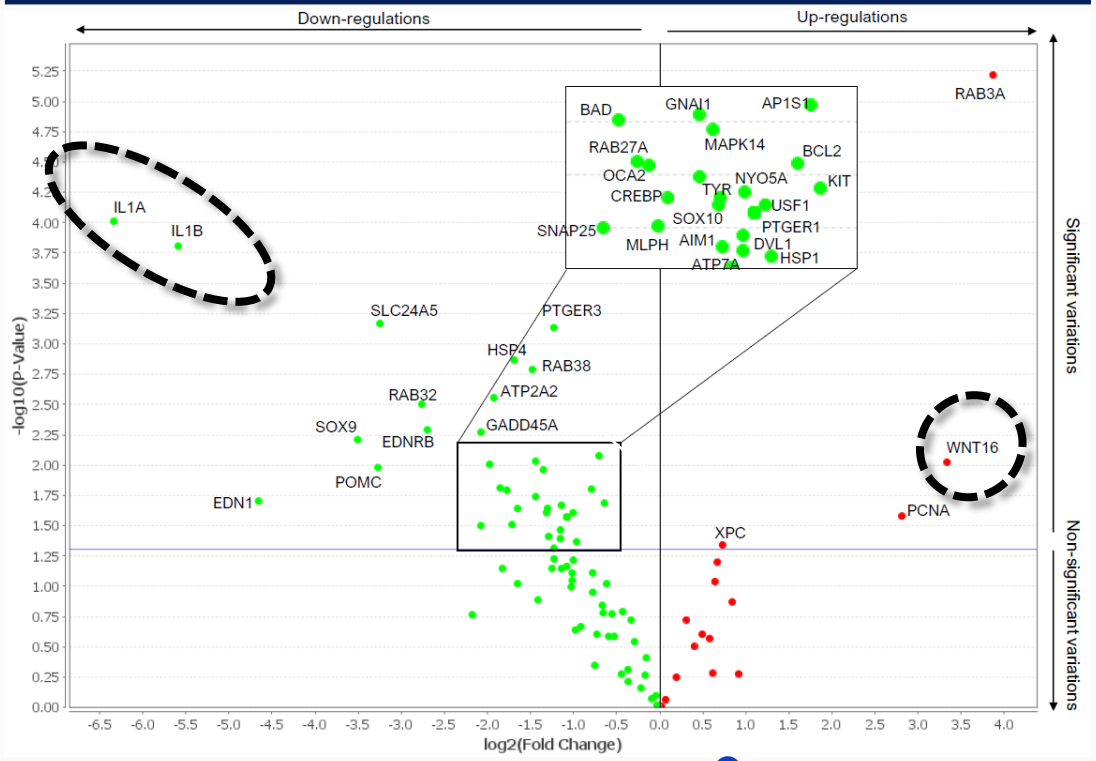
Clear evidence of melanocyte adhesion disruption, melanocyte detachment and migration through the skin



VYN201 1% prevents detachment and subsequent loss of melanocytes from the basal layer implying that E-cadherin adhesion is still functional

Keratinocytes (blue), melanocytes (green)

Stimulated and VYN201 1% treated



Significant downregulation of cytokines IL6, IL1A and IL1B and TNFa and upregulation of the WNT pathway (Wnt16)

TRV: tyrosinase-related protein 1 (important enabler of melanogenesis)

VYN201: Phase 1 Proof-of-Concept

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VYN201: Phase 1b Study in Active Vitiligo Patients

Study Design

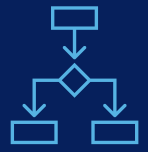
Treatment on the face and target lesion on trunk of active vitiligo patients for up to 16 weeks of QD treatment

- **N = up to 30: 3 cohorts, evaluating 0.5%, 1.0% and 2.0% strengths**
- Safety assessments include TEAEs, pharmacokinetics and local skin tolerance
- Exploratory efficacy assessments include F-VASI, biomarkers and photography

Key inclusion/exclusion criteria:

- Subjects with a clinical diagnosis of active non-segmental vitiligo. An active vitiligo lesion is defined as evidence of hypochromic areas / borders and/or confetti-like depigmentation and/or peri-lesional inflammation and/or Koebner phenomenon.
- Facial-Vitiligo Area and Severity Index Score (F-VASI) of ≥0.5.
- Two contralateral active vitiligo target lesions on non-facial anatomical areas. Non-facial target lesion areas should not include hands, wrists, feet, or elbows.
- The presence of leukotrichia should not exceed 50% of the full face or 50% of each non-facial target lesion.

Primary objectives of Phase 1b:



1. **Assess safety, tolerability and pharmacokinetics**
2. **Evaluate VYN201's ability to arrest the progression of depigmentation in active vitiligo patients**
3. **Identify early evidence of repigmentation**
4. **Inform dose level / dose regimen of Phase 2b dose-ranging study**

F-VASI = Facial Vitiligo Area Scoring Index

Vitiligo Disease Activity within PoC Study Designs

Patient Population and Asset Development Status

	Disease Activity	Status
VYN201 P1b *(VYNE)*	• **Active Only**	• PoC achieved • Phase 1b completed
Litfulo® (ritlecitinib) P2b[1] *(Pfizer)*	• **Active Only**	• Pfizer currently enrolling P3 study evaluating 50 mg QD dose in active & stable disease
Povorcitinib P2b[2] *(Incyte)*	• **Active & Stable**	• Incyte preparing for Phase 3 program
Opzelura® (ruxolitinib) P2b[3] *(Incyte)*	• **Active & Stable**	• 1.5% BID dose approved in the U.S. (July 2022) and EU (April 2023)
Rinvoq® (upadacitinib) P2b[4] *(AbbVie)*	• **Active & Stable**	• Phase 2b completed

VYNE expects to enroll patients with <u>active and stable</u> disease in P2b study

Patients with Active Disease Will Continue to Depigment in Areas that Show High Activity without Therapy[5]

Fig 1:
Vitiligo of the hand with confetti-like depigmentation

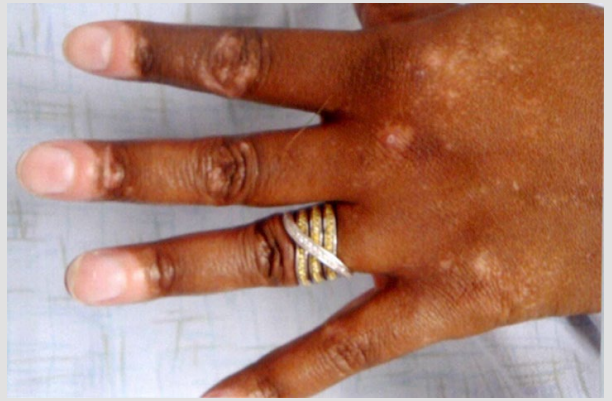
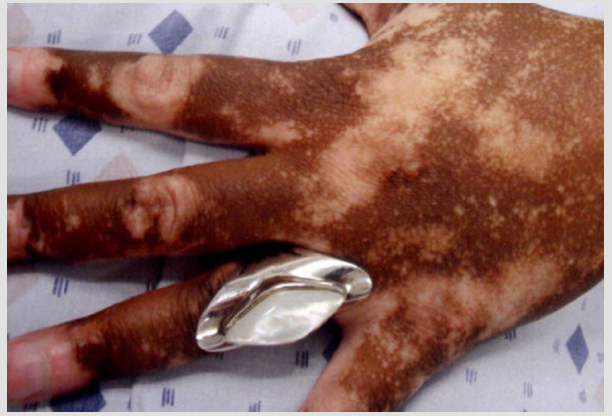


Fig 2:
16 weeks later
Showing extension of depigmentation and new areas of confetti-like depigmentation



Physicians expect patients with active disease to be more difficult to treat

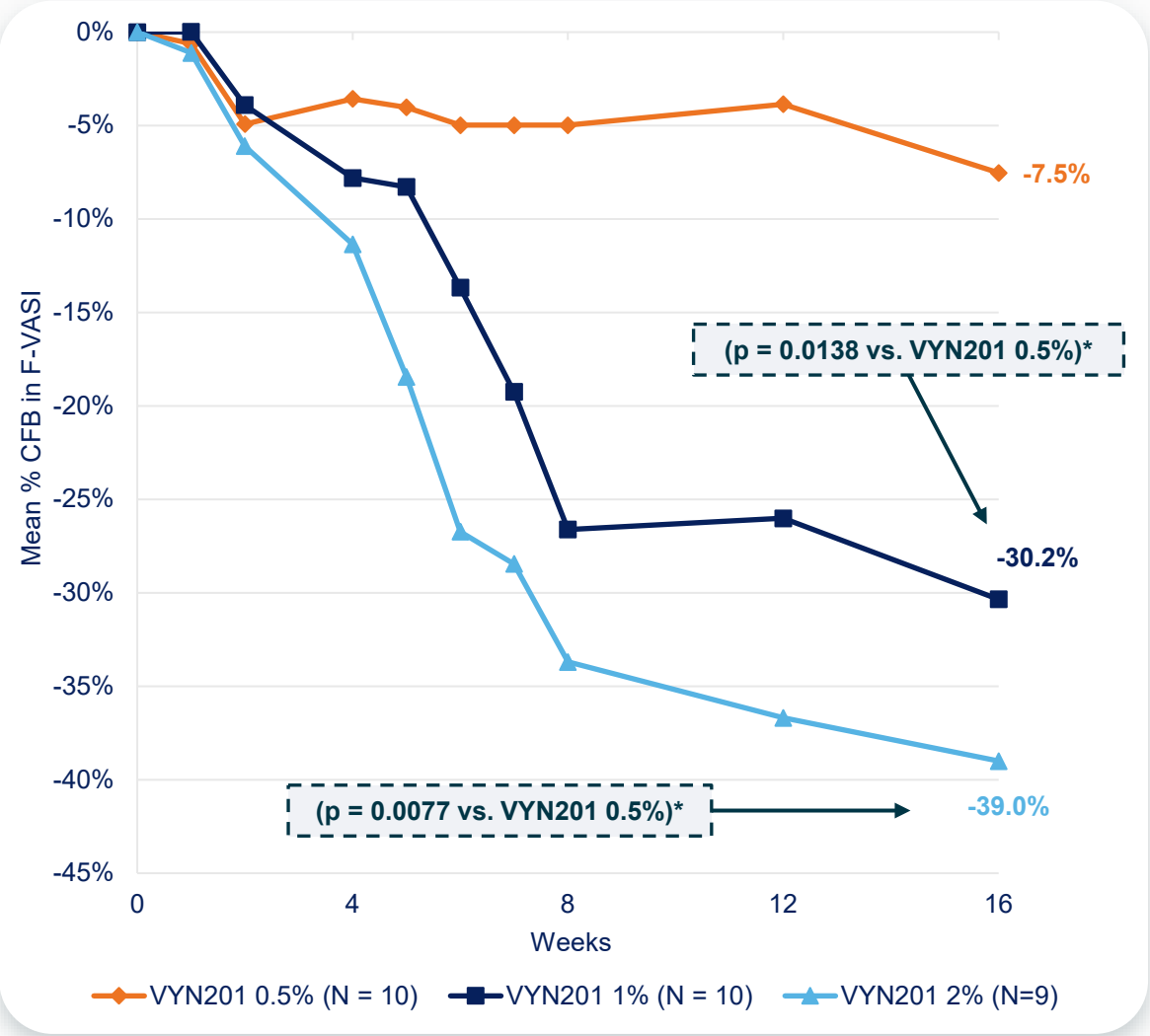
Source: Data on file; 1. NCT03715829; 2. NCT04818346; 3. NCT03099304; 4. NCT04927975; 5. Sosa et al, J Am Acad Dermatol 2015

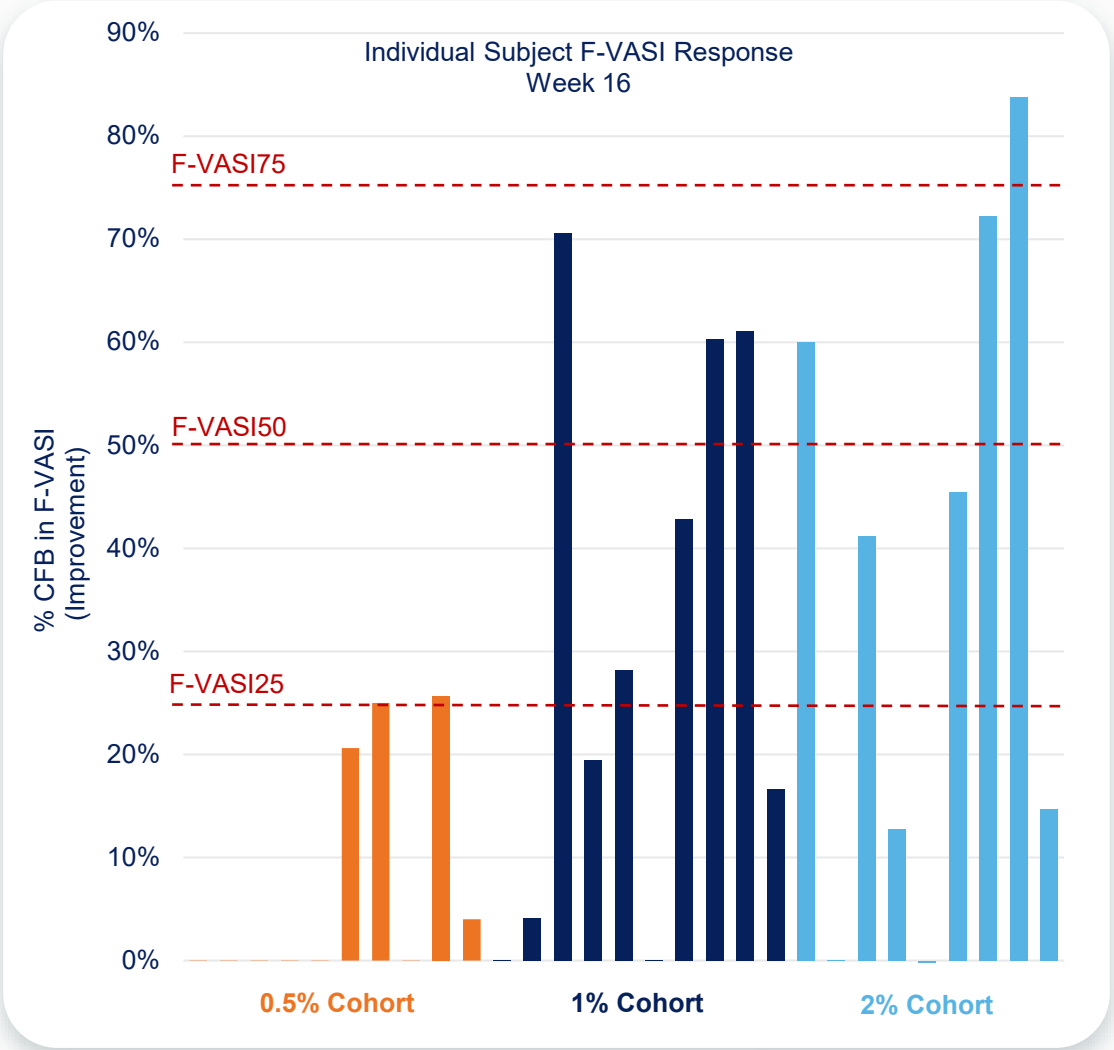
Baseline Demographic and Clinical Characteristics

	0.5% Cohort (N=10)		1% Cohort (N=10)		2% Cohort (N=9)		Total (N=29)	
Age - year mean	49.2		53.2		57.0		52.9	
Age group - no. / %	0	0%	0	0%	0	0%	0	0%
12-17	0	0%	0	0%	0	0%	0	0%
18-64	9	90%	8	80%	8	89%	25	86%
>=65	1	10%	2	20%	1	11%	4	14%
Female sex - no. / %	6	60%	7	70%	7	78%	20	69%
Race or ethnic group								
Hispanic or Latino	0	0%	2	20%	7	78%	9	31%
Not Hispanic or Latino	10	100%	8	80%	2	22%	20	69%
Fitzpatrick Skin type - no. / %								
I	0	0%	0	0%	0	0%	0	0%
II	5	50%	4	40%	1	11%	10	34%
III	1	10%	3	30%	3	33%	7	24%
IV	3	30%	2	20%	4	44%	9	31%
V	0	0%	0	0%	1	11%	1	3%
VI	1	10%	1	10%	0	0%	2	7%
F-VASI mean / (min-max)	1.34	(0.54-3.21)	1.14	(0.51-3.36)	0.83	(0.51-1.92)	1.11	(0.51-3.36)
Disease stability - no. / %								
Active / Progressive	10	100%	10	100%	9	100%	29	100%
Stable	0	0%	0	0%	0	0%	0	0%

Promising Onset of Action and F-VASI Response

VYN201 Phase 1b: QD Treatment in 100% active disease study population

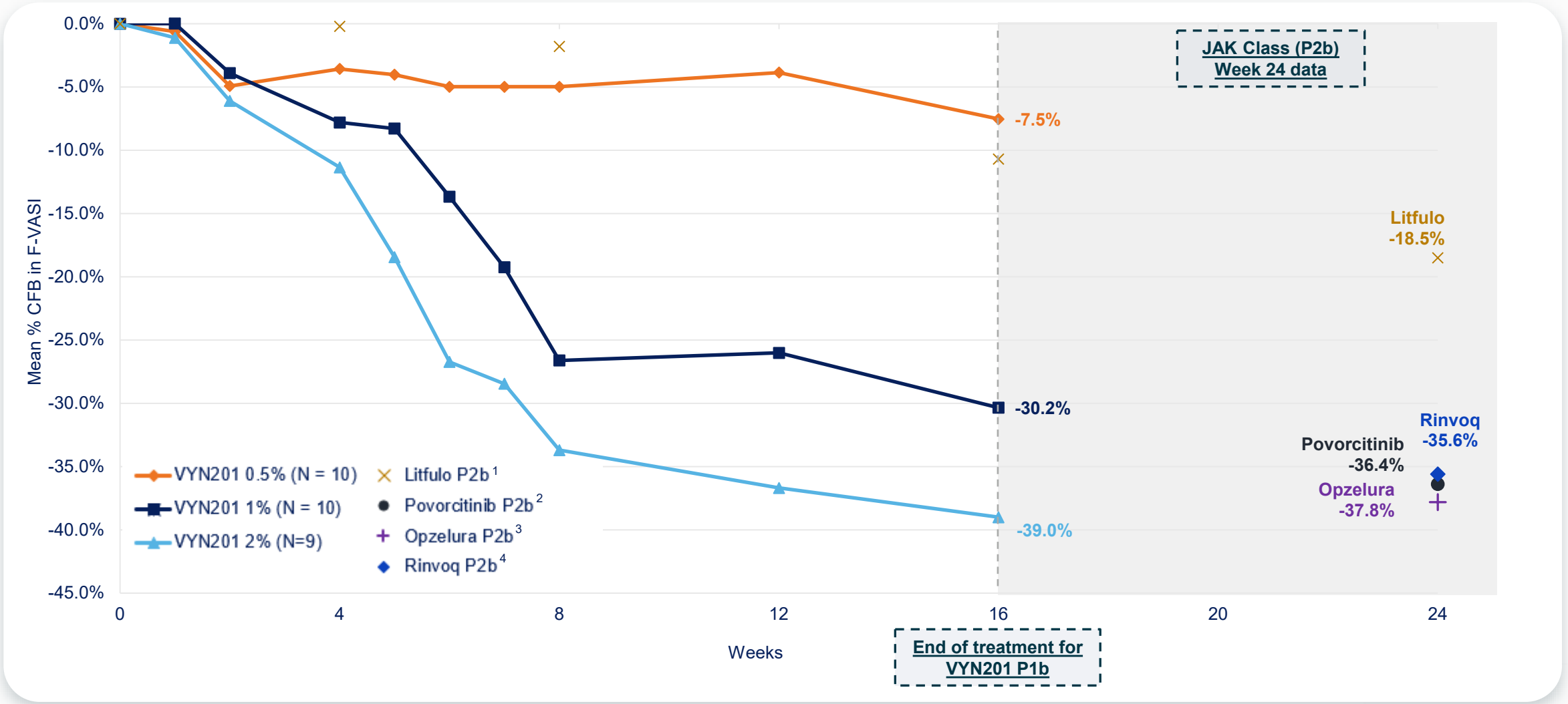




*% CFB T-test based on latest observed case (LOCF)

Demonstrated Competitive Efficacy at 16 Weeks vs. JAK Class at 24 Weeks

VYN201 Phase 1b: QD Treatment in 100% active disease study population



Note: Data is not based on Head-to-Head comparisons; Source: Clinicaltrials.gov; Study Publications: 1. NCT03715829 (LS mean %CFB for 50 mg QD); 2. NCT04818346 (LS mean %CFB for 45 mg QD); 3. NCT03099304 (LS mean %CFB for 1.5% BID); 4. NCT04927975 (LS mean %CFB for 11 mg QD); *% CFB T-test based on latest observed case (LOCF)

Preclinical & Clinical Data Highlight Potential for Differentiated Product Profile

Characteristic	VYN201		Opzelura (Ruxolitinib) Cream 1.5%	Litfulo (Ritlecitinib) 50mg[1]	Povorcitinib 45mg[2]
	1%	2%			
Novel MOA / JAK Class Alternative	✓		✗	✗	✗
Targeted Dosing Posology	QD		BID	QD	QD
Rapid Onset of Action	✓		Moderate	✗	Moderate
Efficacy, % CFB F-VASI, Week 16	**100% active disease study**		**Active & stable disease study** P2b: -37.8 (Week 24)[3]	**100% active disease study** -1.8 (Week 8) -18.5 (Week 24)	**Active & stable disease study** -36.4 (Week 24)
	-30.2	-39.0			
Efficacy, % F-VASI25, Week 12[5]	40.0	55.6	P3: 27.3[4]	-	-
Efficacy, % F-VASI50, Week 12[5]	20.0	33.3	P2b: 21.2[3] P3: 29.2[4]	0.0 (Week 8) 15.4 (Week 24)	25.0
Potential to Upregulate WNT Pathway	✓		✗	✗	✗
Safety Precaution	-		✗ "Black Box"	✗ "Black Box"	✗ Expect "Black Box"
Systemic Exposure	Low (Cmax <1 nM)		Cmax/AUC: 449nM / 3215nM	-	-

Data is not based on Head-to-Head comparisons
Source: Clinicaltrials.gov; Data on file 1.NCT03715829 2. NCT04818346; 3. NCT03099304; 4. Pooled analysis TRuE-V1 and TRuEV2 Incyte Corporate Presentation dated July 19, 2022;
5. Week 16 data for JAK class not available;

Demonstrated Favorable Safety & Tolerability Profile

Adverse Events

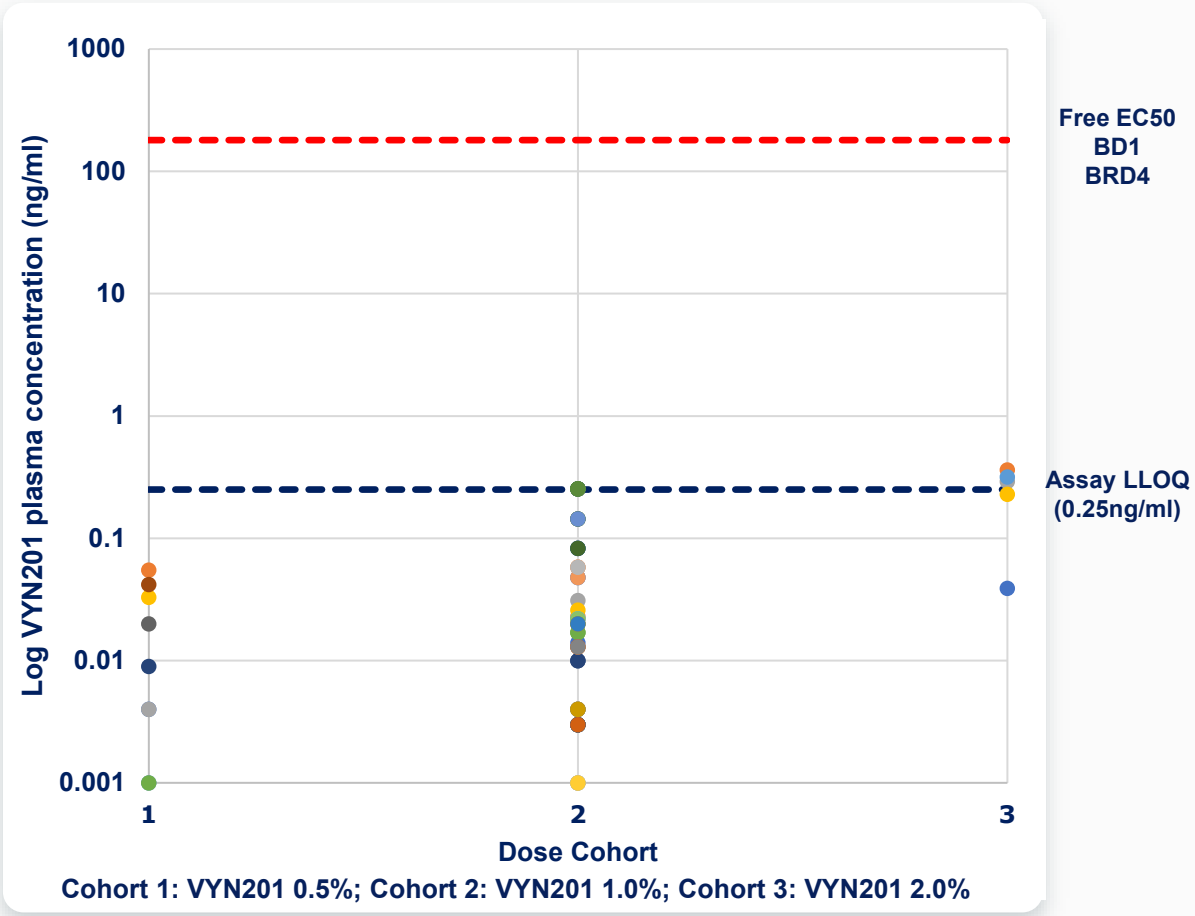
- **No** serious adverse events reported
- **No** treatment related discontinuations
- **All** treatment emergent adverse events classified as **mild (>70%) or moderate**; **no** severe AEs
- **No** dose/exposure-dependent increases in AEs
- **No** significant alterations in clinical safety lab parameters

Local Skin Tolerability

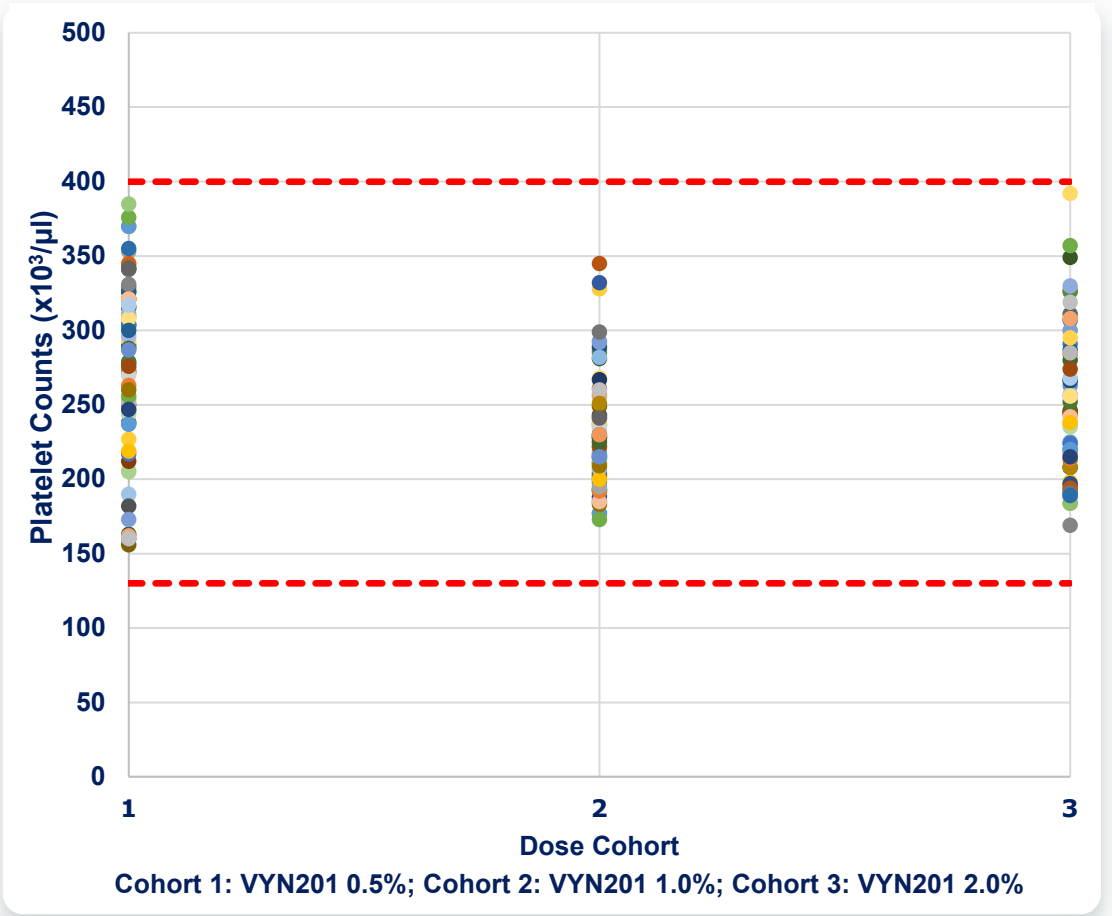
Assessment	Mean Score Range 0 (None) to 3 (Severe)
Burning/Stinging	0.26
Scaling	0.15
Dryness	0.22
Pruritus	0.14
Erythema	0.29
Hyperpigmentation	0.10

VYN201 Phase 1b: Low Systemic Exposure in Vitiligo Subjects Correlates with No Impact on Platelet Counts

Available data for treatment up to 16 weeks supports "soft" drug approach for topical pan-BD BET inhibitor



Cohort 1: VYN201 0.5%; Cohort 2: VYN201 1.0%; Cohort 3: VYN201 2.0%



Cohort 1: VYN201 0.5%; Cohort 2: VYN201 1.0%; Cohort 3: VYN201 2.0%

- VYN201 concentrations markedly below free EC50BD1 BRD4 at all dose levels for available data for treatment up to 16 weeks
- Assay LLOQ is 720-fold lower than the free $EC50_{BD1\ BRD4}$ for VYN201

- All platelet counts remain within normal range
- No trends suggestive of reducing counts by treatment duration
- Similar lack of effect on neutrophils, eosinophils, lymphocytes, basophils and monocytes (data not shown)

Data available as of 11/8/23 LLOQ = Lower Limit of Quantification

Key Takeaways from VYN201 Phase 1b Results

PoC Achieved

- Significant clinical response shown with rapid onset of action
- Clear evidence of dose response

- Efficacy data suggest potential to be category leader
- Favorable efficacy results and onset of action compared with the JAK competitive landscape in a more difficult to treat patient population (active disease vs. stable disease)

- Demonstrated favorable safety and tolerability profile to date
- Low systemic exposure levels support “soft” drug design

- Believed to be first clinical demonstration of BET inhibitor’s effect in autoimmune disease[1]

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

VYNE™ THERAPEUTICS

VYN201 Phase 2b Study Design Summary

Randomized, double-blinded, vehicle-controlled Phase 2b trial with separate active treatment extension phase evaluating the efficacy, safety & pharmacokinetics of VYN201 in the treatment of non-segmental vitiligo

Trial size: N=~150 to 200 patients with non-segmental vitiligo (including patients with active and stable disease)
N=50 / arm, evaluating up to 4 arms of once-daily treatment (vehicle, low, mid, high)

Duration: 24 weeks with extension to 52 weeks

Key efficacy endpoints:

Primary:	Proportion of subjects achieving FVASI50 at Week 24 vs. Vehicle
Secondary:	Proportion of subjects achieving TVASI50 at Week 52
	Proportion of subjects achieving FVASI25/75 at Week 24 and 52
	%CFB in FVASI score at Week 24 and 52

Key safety assessments:

- Treatment emergent adverse events
- Local skin tolerability assessments
- Clinical laboratory assessments (hematology, chemistry, urinalysis, FSH), Physical exam/vitals, PK

Current estimate; Subject to concurrence from the FDA

VYN202: BD2 selective BET inhibitor

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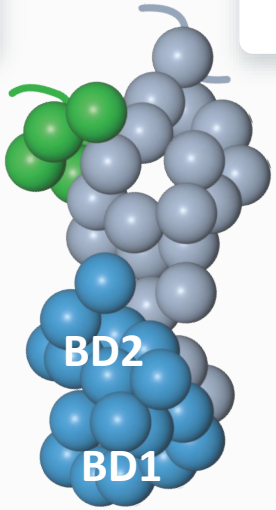
VYNE's Drug Design Strategy

Optimize benefit/risk profile of BET inhibitors to target autoimmune diseases

VYN201
Pan-BD BET Inhibitor

Maximize local effect & minimize systemic exposure

- Tissue targeted administration routes & formulations
- Soft drug / drug delivery strategies to reduce impact of BD1 inhibition on steady-state gene regulation



VYN202
BD2-Selective BET Inhibitor

Improve efficacy and tolerability through BD2-selectivity

- Class-leading BD2 vs. BD1 selectivity for systemic administration
- BD2 activity more relevant to inflammatory gene expression
- Minimize BD1 inhibition to protect against steady-state gene disruption

Gilan et al, Science. 2020 April 24; 368(6489): 387–394

 Dawson et al, Science 2020; Belkina, Nikolajczyk & Denis, J. Immunol. 2013

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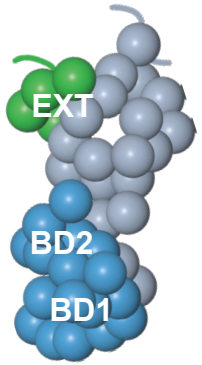
Maximizing On-target Potency vs. BD2 and Minimizing Affinity to BD1 May Be The Key to Optimizing the Benefit/Risk Profile of BET Inhibitors for Autoimmune Diseases

VYN202 is believed to be the most potent and BD2-selective BET Inhibitor in 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

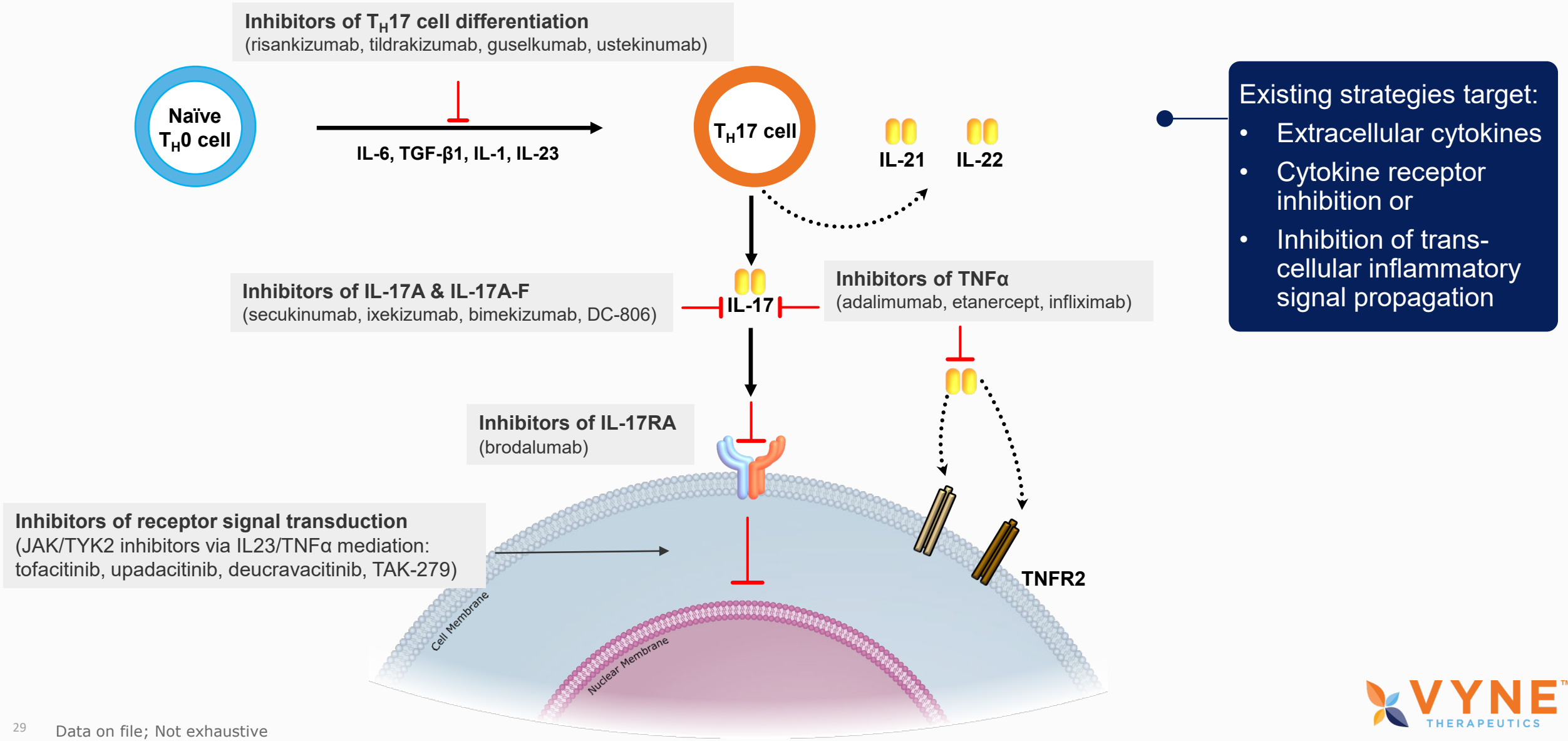
BD1 regulates "housekeeping" gene activity

Compound ID	Potency vs. BD2* (nM)	Selectivity** (BD1/BD2)
VYN202 (VYNE)	**<**	**>>>>**
NUV-868 (Nuvation)[2]	2	1,460x (FRET)
ABBV-744 (AbbVie)[3]	28	753x (FRET)
GSK620 (GSK)[4]	79	220x
Pelabresib (Constellation)[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 (May 2023); 3. Faivre et al 2020; 4. Delmont et al 2020; 5. Wang et al 2017 6. Kraut et al 2018; Data on file

Strategies to Control Dysregulated T_H17 Immune Cell Activity



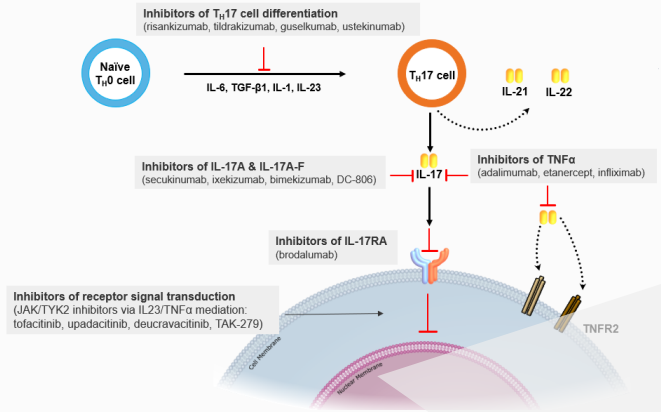
Existing strategies target:

- Extracellular cytokines
- Cytokine receptor inhibition or
- Inhibition of trans-cellular inflammatory signal propagation

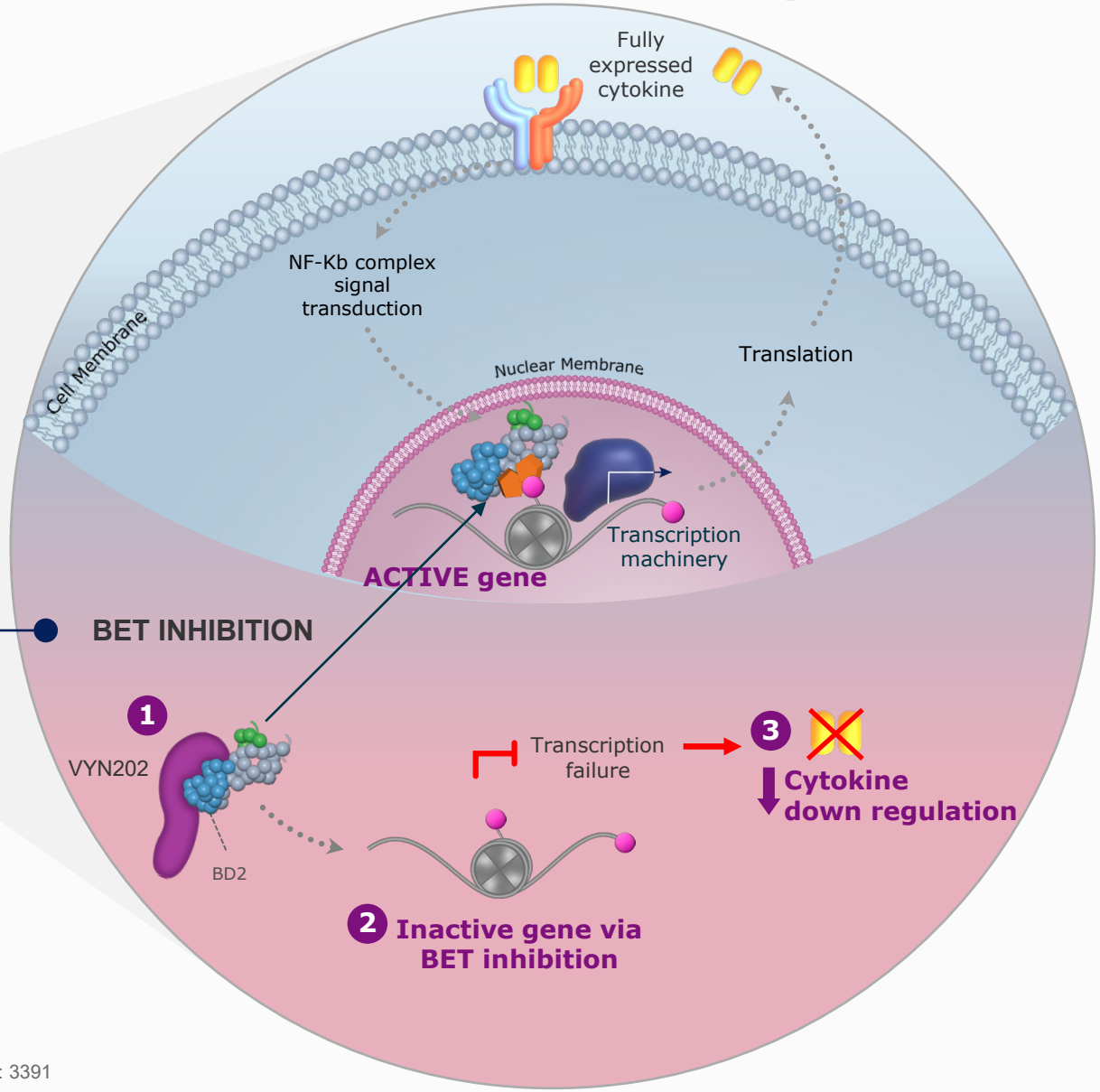
Data on file; Not exhaustive

VYNE™ THERAPEUTICS

BET Inhibitors Disrupt Inflammatory Gene Transcription in T Cells to Directly Address the Complex Signaling of Immuno- & Fibro-inflammatory Diseases



Clinical PoC of BET inhibition in I&I disease demonstrated in VYN201 P1b vitiligo trial

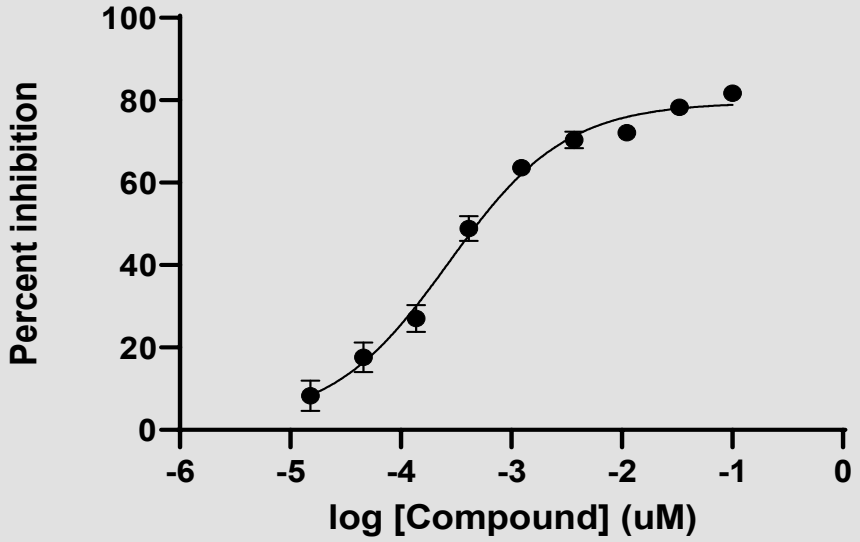


Adapted from Gonzalez-Gay et al, Autoimmunity Rev, (2020) 19: 102429 and Rusinol and Puig, Int J Mol Sci, (2023) 24: 3391

Demonstrated Potency Against Th17 Cytokines

VYN202 Potency vs. IL-17A compares favorably to Secukinumab and DC-806

VYN202 Potency vs. IL-17A



Therapeutic Agent	$IC50_{IL17A}$ (nM)
VYN202 (VYNE)	0.27
Secukinumab (Cosentyx - NVS):	0.37
DC-806 (DICE/LLY)	5.7

Cytokines were analysed by ELISA with media supernatant from cultured human PBMCs activated with anti-CD2, CD3 & CD28 antibodies in the presence or absence of compounds for 72h.

Source: Data on file; Summary basis of approval for Cosentyx, pharmacology review, CDER, FDA, August 2014; Dice Therapeutics Corporate Presentation March 2023

Minimal Inhibition on Key Innate Immune Chemokine Demonstrates Selectivity of Cytokine Expression (IL-17A and IL-22 vs. CXCL10)

Cytokine	VYN202 IC_{50} (nM)	Selectivity vs. CXCL10
IL-17A	0.27	>13,000
IL-22	0.21	>17,000
CXCL10	3637	-

- **VYN202 significantly more potent against Th17 Cytokines vs. CXCL10**
- CXCL10 interacts with CXCR3 to attract Th1 cells, eosinophils, monocytes, and NK cells to sites of inflammation and is known to be an important part of host defense mechanism

Analysed by ELISA with media supernatant from human PBMCs stimulated with IFN-γ for 24h.

Source: Data on file

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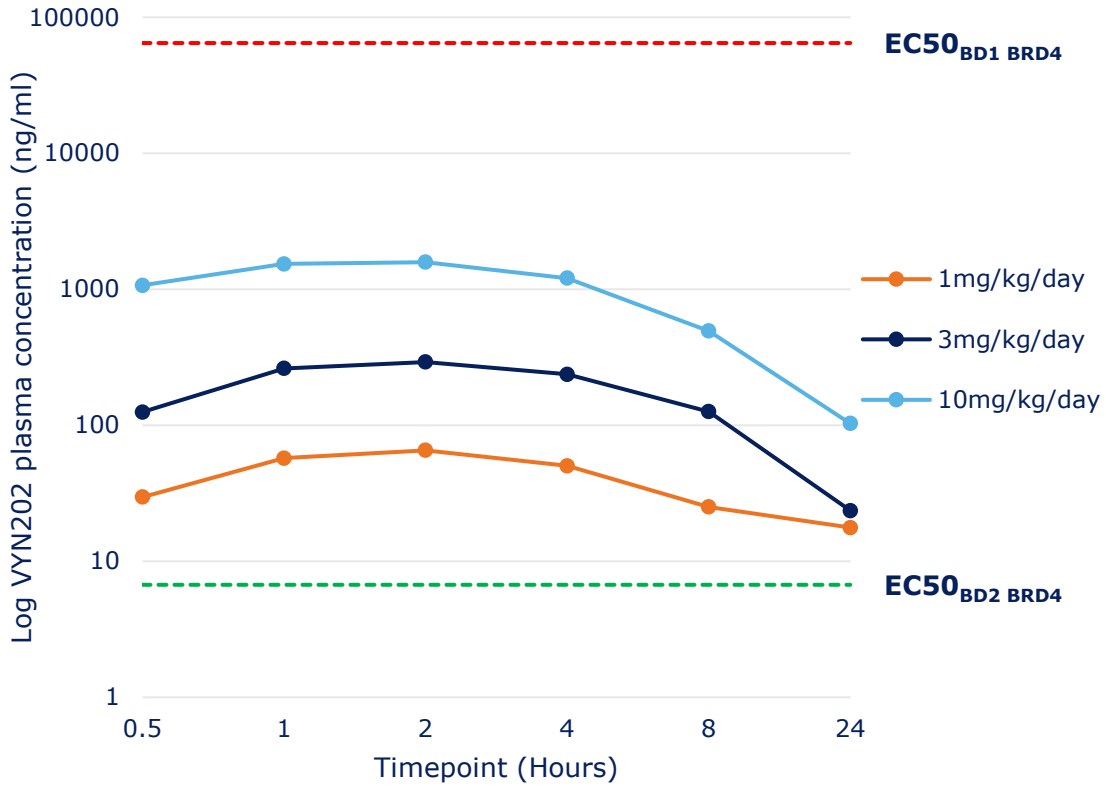
Preclinical Safety Data

VYNE™ THERAPEUTICS

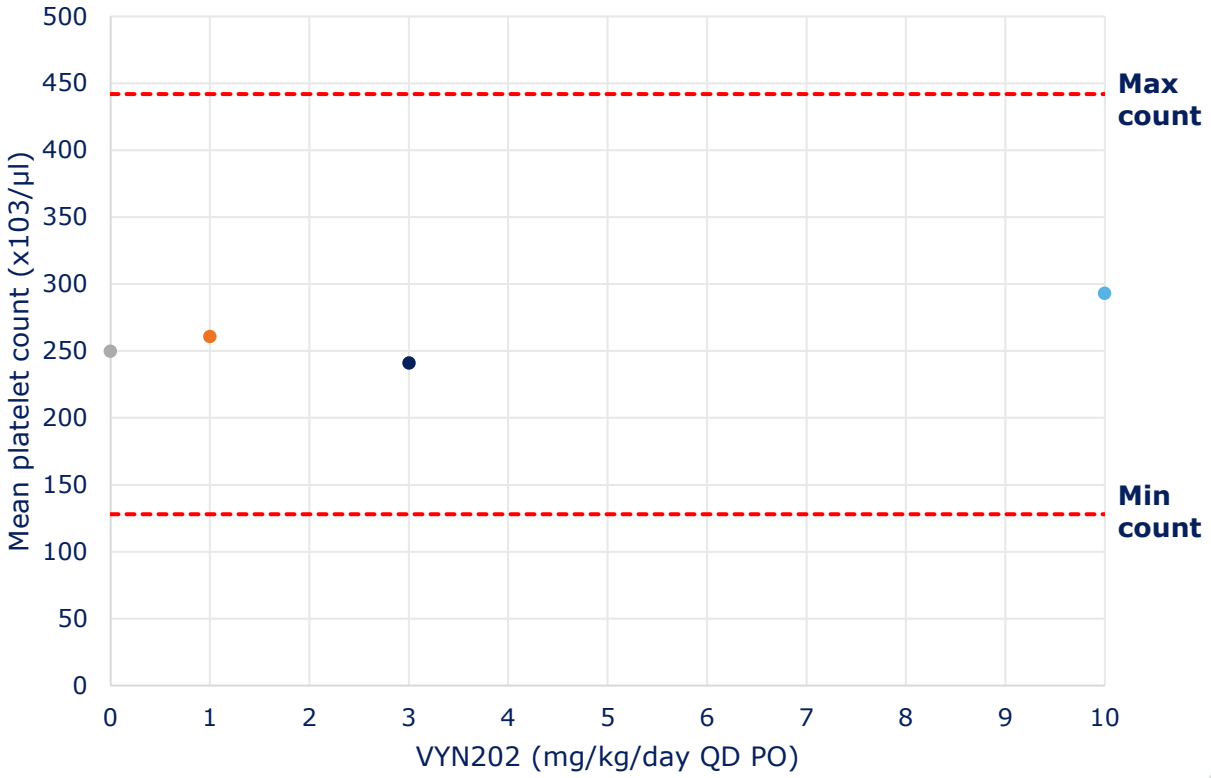
Dog Toxicokinetics & Effect on Hematopoietic system

- VYN202 exposure significantly above free $EC50_{BD2\ BRD4}$ at 1,3 & 10mg/kg QD for 24 hours
- No effect on platelet counts

VYN202 Exposure after 14 Days of Treatment at 1, 3 and 10mg/kg QD PO



Effect of VYN202 on Platelet Counts (Day 15)



- VYN202 exposure above free $EC50_{BD2\ BRD4}$ at all dose for 24hrs
- No exposure differences between males and females

- No evidence of reduced or reducing platelet counts

Effect on Gastrointestinal (GI) System

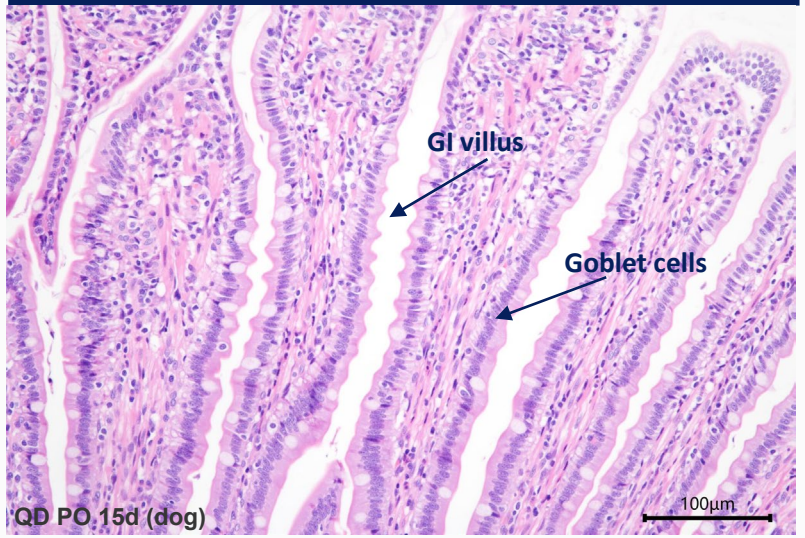
Compared to pan-BD BET inhibitors

Oral pan-BD BET inhibitors (like ABBV-075) are known to negatively impact GI mucosa via goblet cell toxicity, leading to related gastrointestinal adverse events in the clinic*

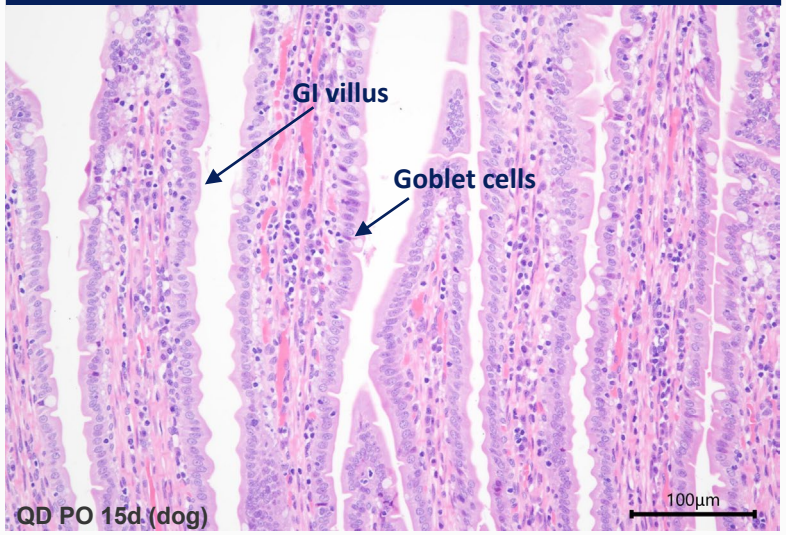
ABBV-075 (Pan-BD BET inhibitor)

Treatment with BD2 selective VYN202 had no effect on GI villus morphology or goblet cell number

VYN202 (BD2 Selective)
Vehicle



VYN202 (BD2 Selective)
10mg/kg



* Faivre EJ et al, Nature, 578, 306-310 (2020)

Images for VYN202 representative from histopathology of the duodenum (H&E stain). Comparable results obtained for ileum and jejunum.

Preclinical Efficacy Models

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VYN202: Psoriasis Model

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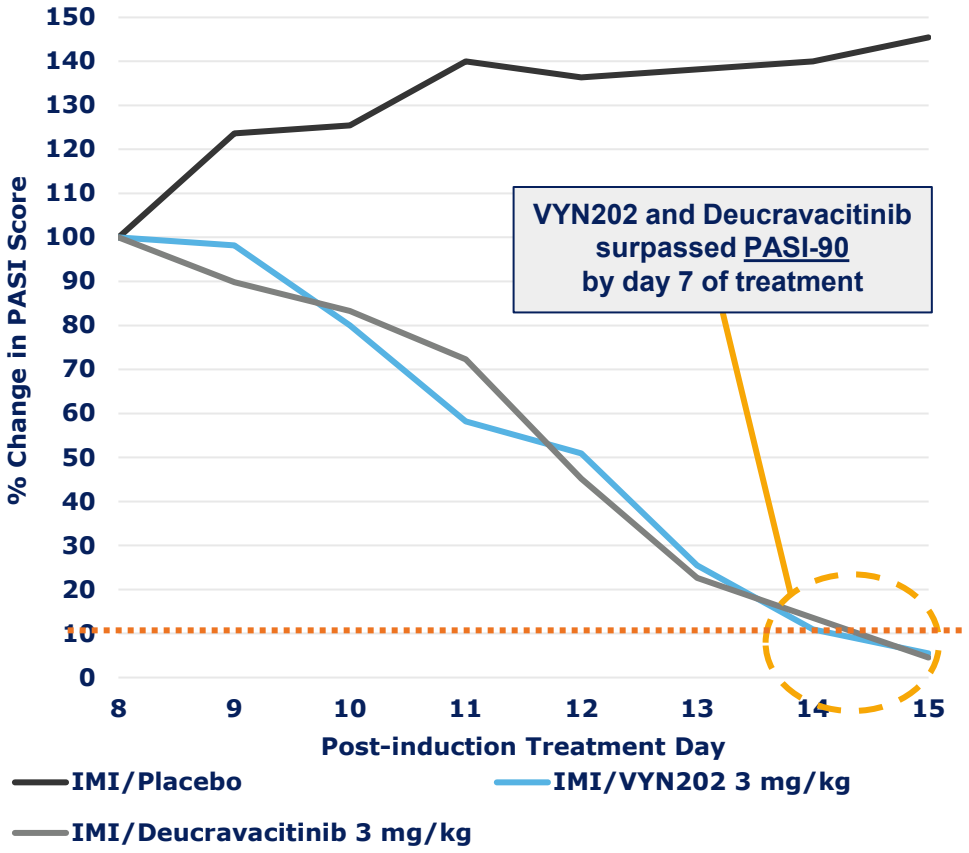
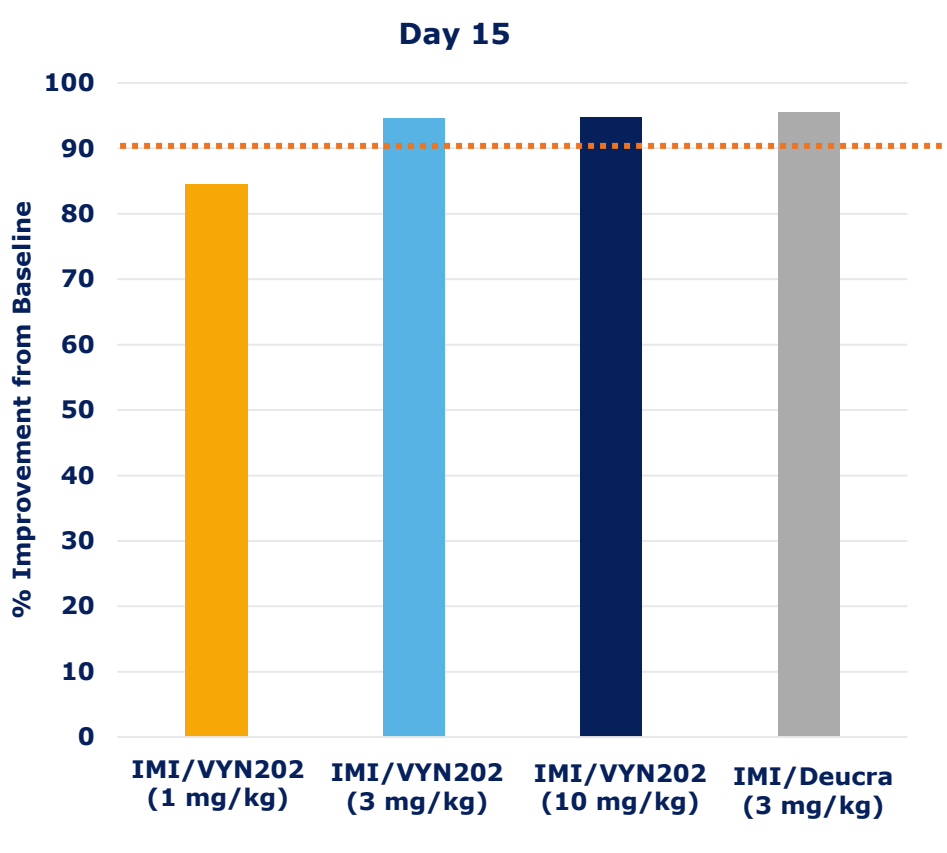
VYN202: Comparable Onset of Action and Efficacy to Deucravacitinib[1]
at Equivalent Dosing in Preclinical *in vivo* Model of Psoriasis

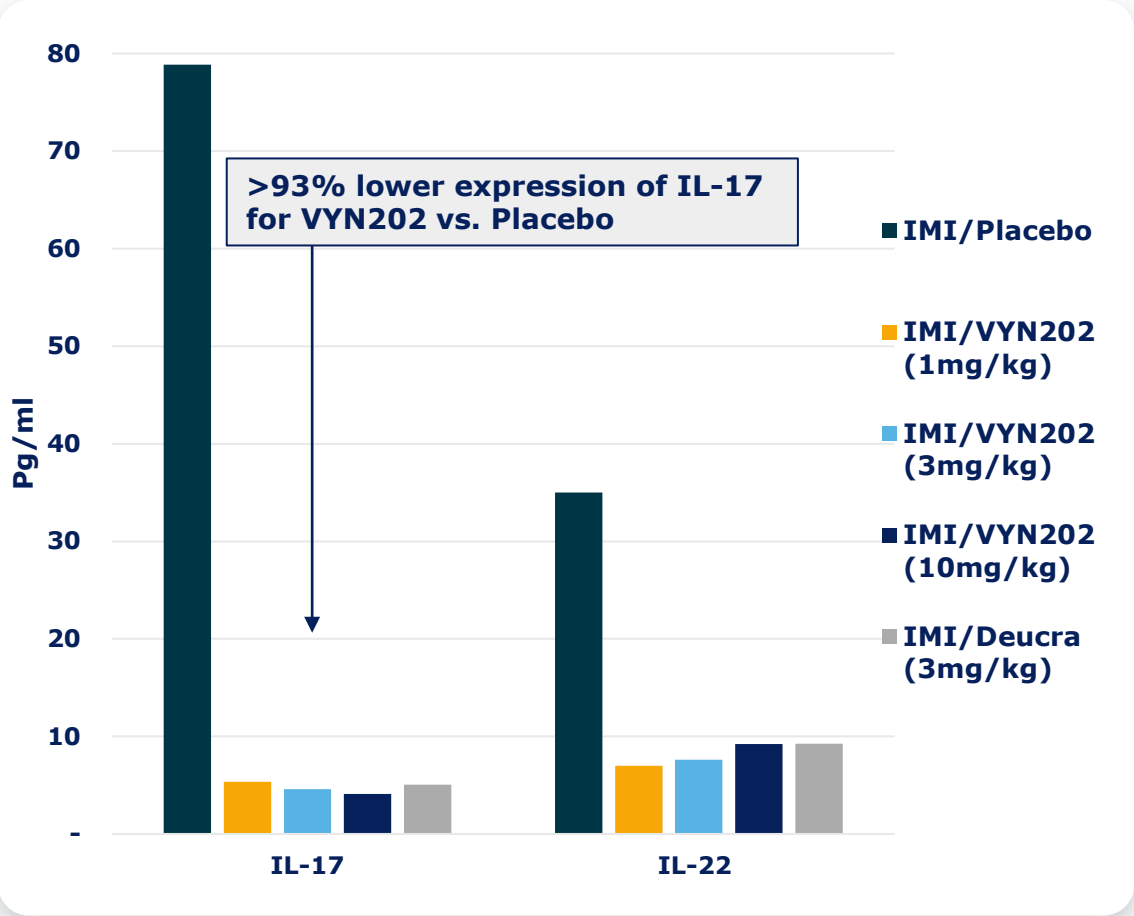
Dorsal depilated BALB-C mice were dosed for 14 days with topical imiquimod cream (Day 1-7: induction phase, Day 8-14: treatment phase). N=8 animals were assigned to each treatment group and received 3 mg/kg of allocated treatment intraperitoneally dosed once-daily on Day 8-14.

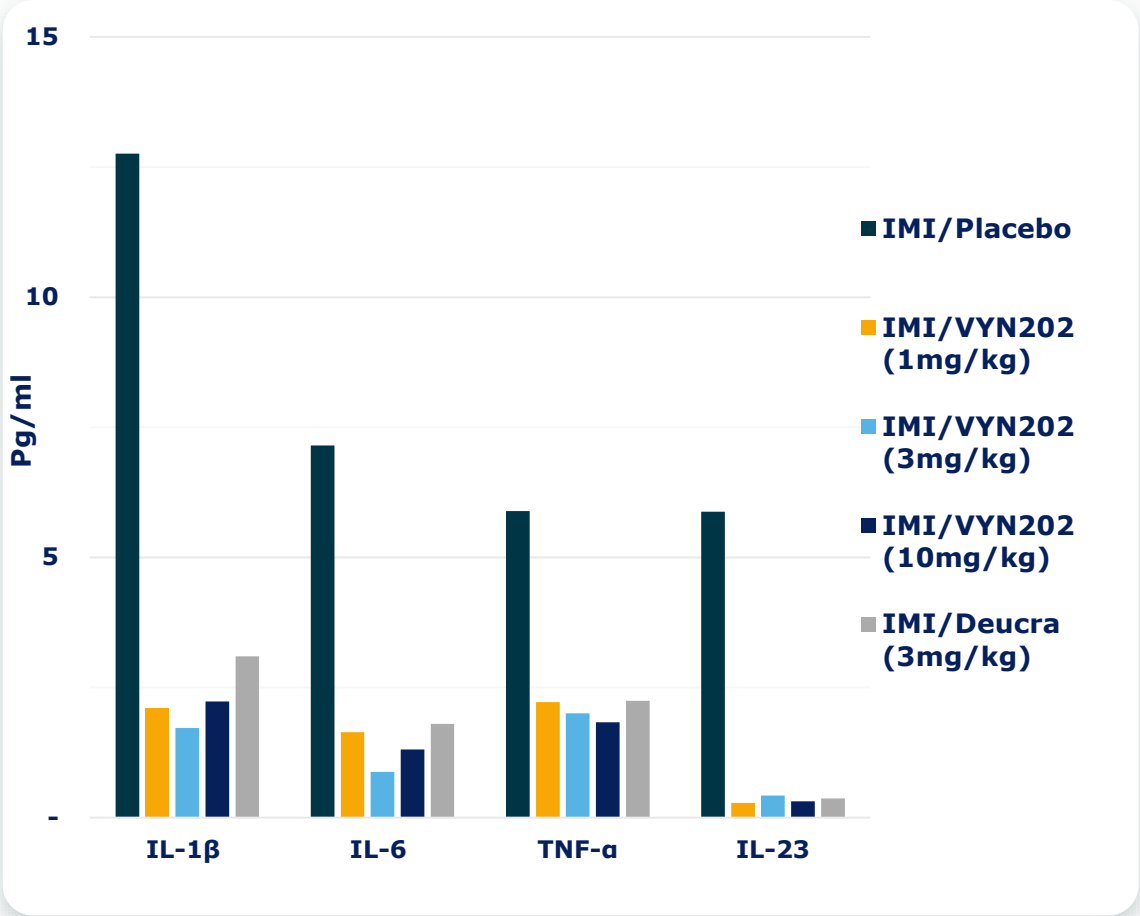




1Sotyktu® (deucravacitinib) was approved in the U.S. in September 2022.
PASI-90 = 90% improvement from baseline in PASI score

VYN202 Reduced Key Cytokines Associated with Pathogenesis of Psoriasis
in Preclinical *in vivo* Model





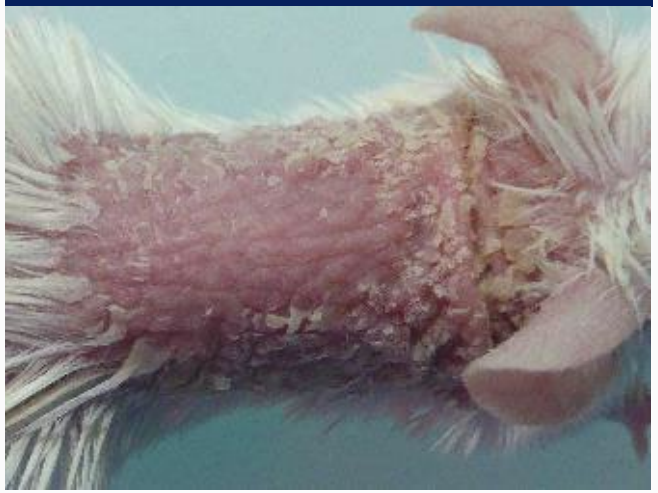
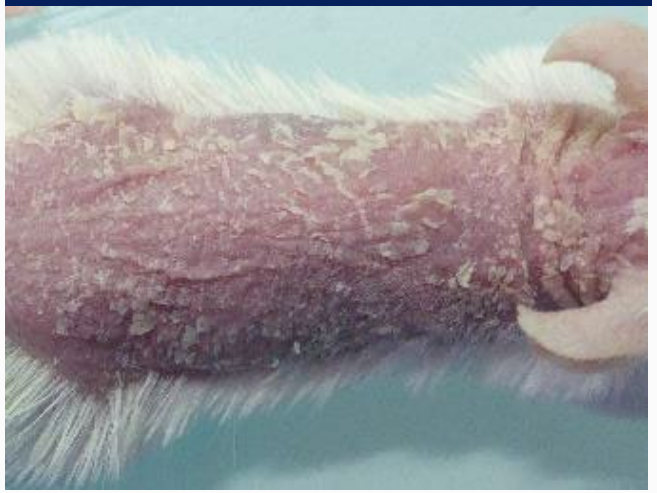
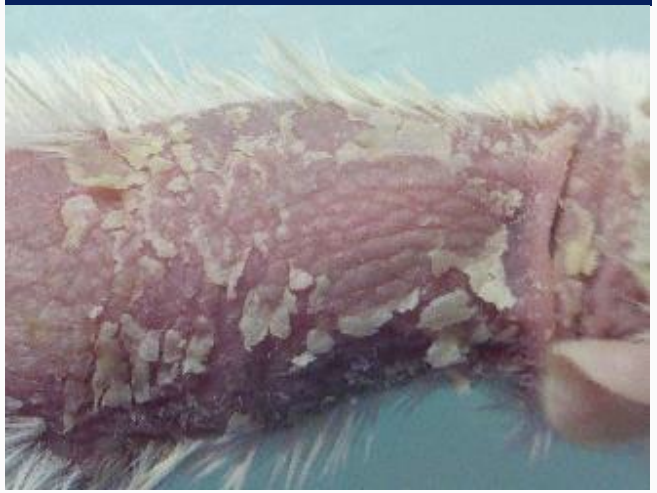
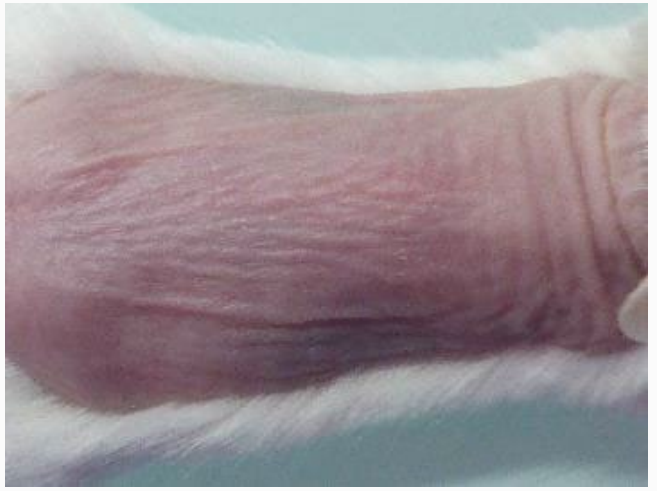
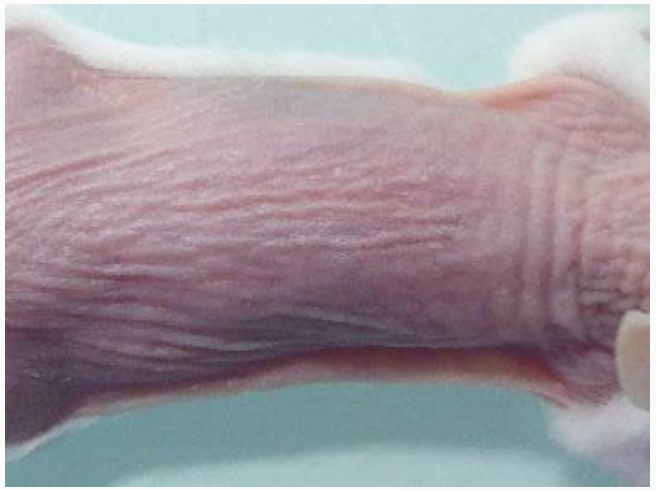
- >93% lower expression of IL-17 at all VYN202 doses compared to placebo

- Marked reduction of other disease related Th17 and Th1 cytokines

IMI = imiquimod

VYN202: Marked Improvement in Clinical Presentation of Disease

Comparable to deucravacitinib in resolving induced dermal inflammation at an identical dose after 7 days of treatment

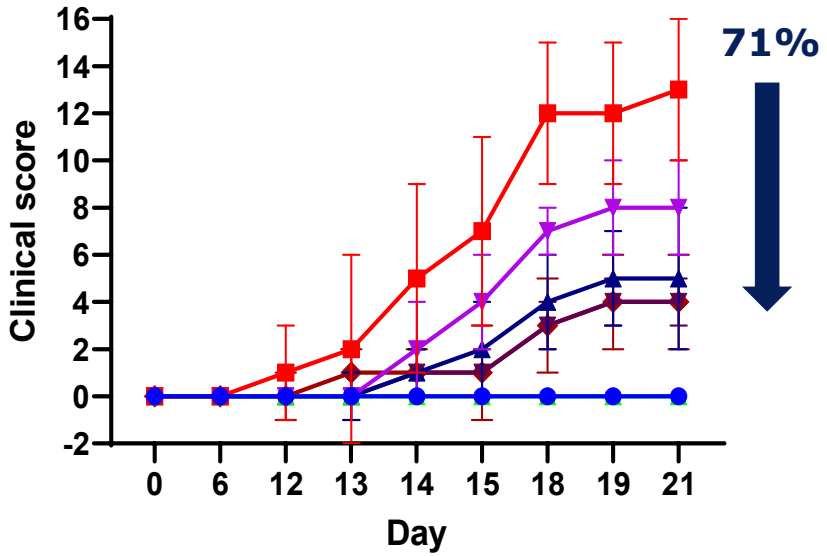
	IMI/Placebo	IMI/VYN202 3mg/kg	IMI/Deucravacitinib 3mg/kg
Day 8 Before treatment			
Day 15 After 7 days of treatment			

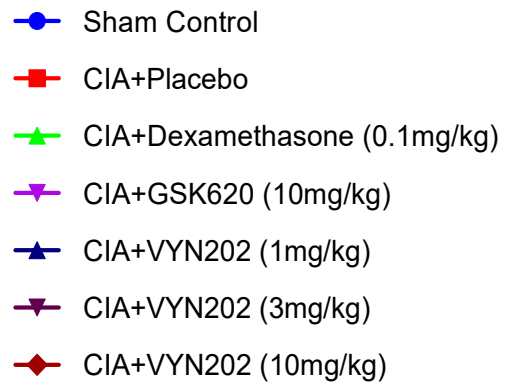
IMI = imiquimod;

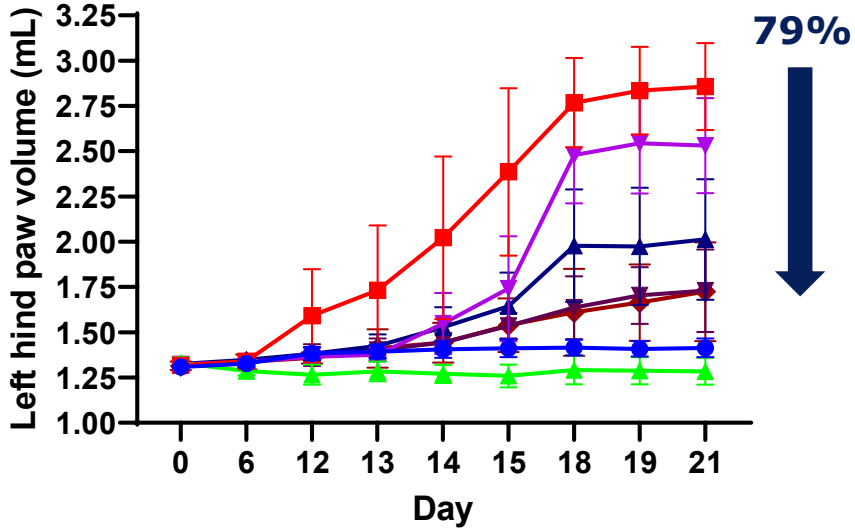
VYN202: Rheumatoid Arthritis Model

VYN202: Collagen-Induced Arthritis Model in the Rat – Arthritis Score

- VYN202 demonstrated highly potent anti-inflammatory activity
- VYN202 statistically superior to GSK620 (BD2-selective BET inhibitor) at all dose levels







- VYN202 10mg/kg PO QD treatment resulted in a 71% lower clinical score and 79% lower paw volume compared to CIA+Placebo control at Day 21
- All VYN202 treatment groups were statistically significantly superior to both CIA+Placebo and GSK620 10mg/kg PO QD controls

Inflammatory arthritis was induced in Lewis rats using a mixture of collagen and CFA by IV injection at Day 0 and was further challenged with a collagen and IFA IV injection at Day 7 (N=8/treatment group). Treatment groups received oral doses QD for 21 days. Clinical score was evaluated for all four limbs with scoring range from 0 (normal) to 4 (extensive signs and symptoms of arthritis); Maximum clinical score: 16

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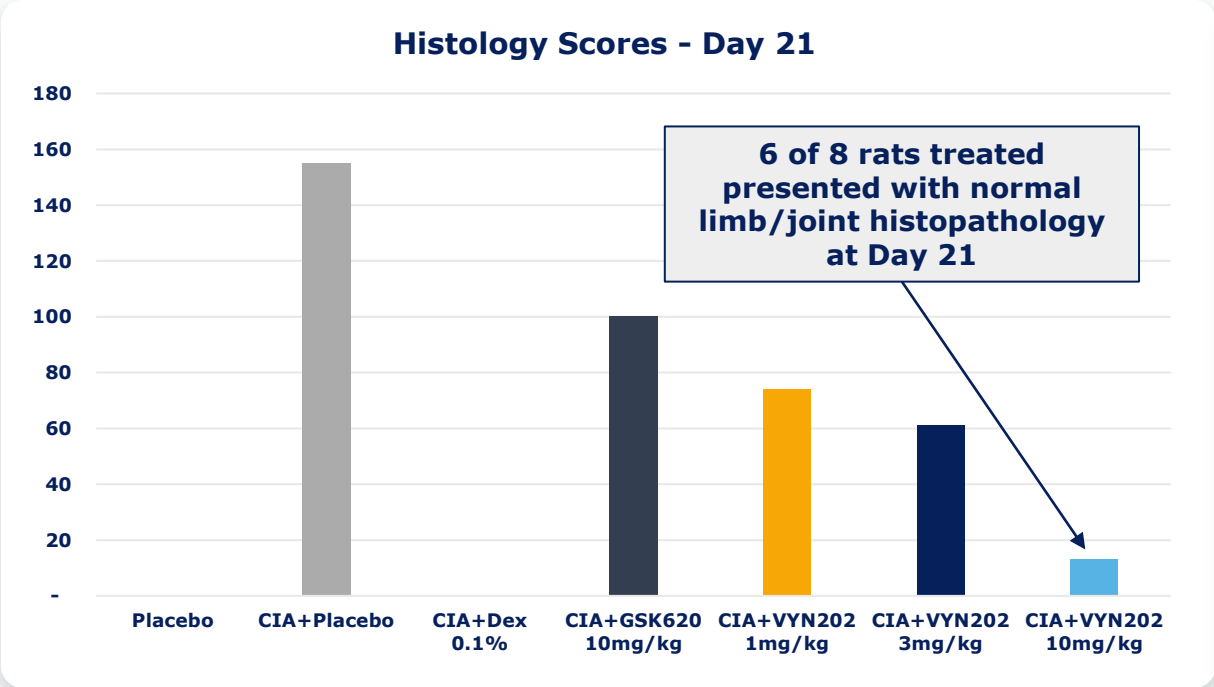
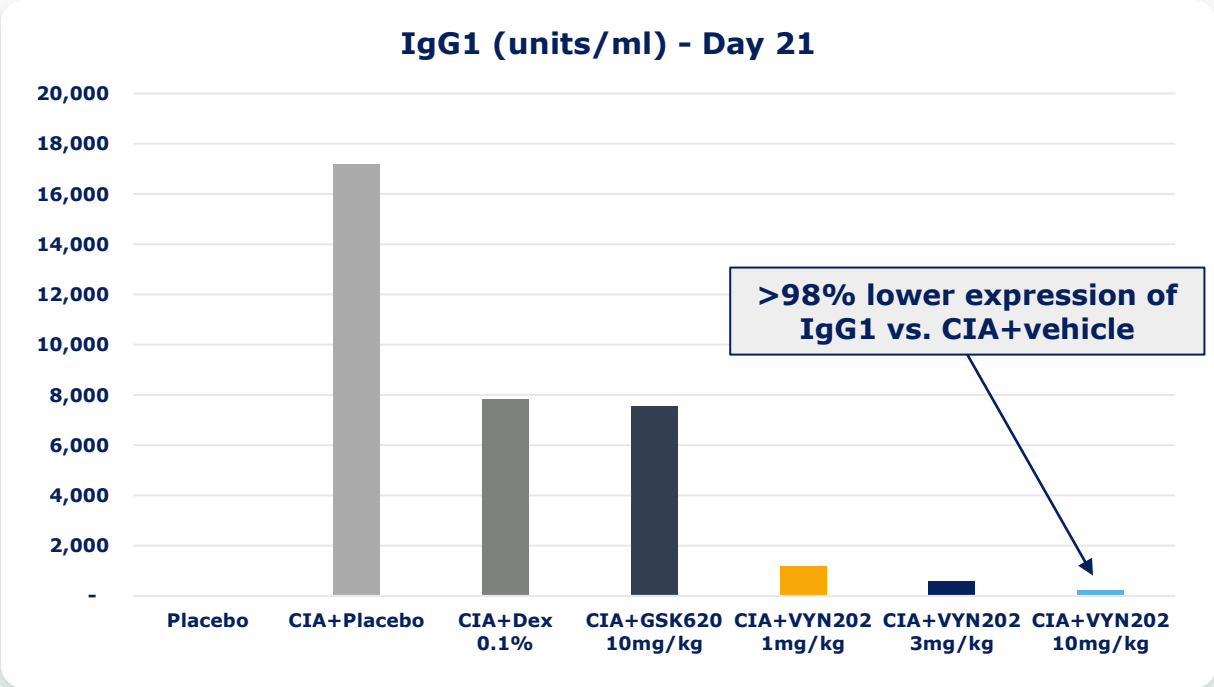
VYN202: Collagen-Induced Arthritis Rat Model – Histology Score & Biomarkers

- Treatment with VYN202 at 10mg/kg PO QD results in near normal joint histopathology
- VYN202 demonstrated near complete inhibition of IgG1* expression at all doses





- CIA+VYN202 treatment resulted in a dose-dependent reduction in severity of arthritic histopathology & was statistically superior to CIA+Placebo and CIA+GSK620 at all doses
- VYN202 10mg/kg PO QD reduced the expression of IgG1 by >98% vs. CIA+Placebo control & was statistically equivalent to Placebo control

*Immunoglobin G1

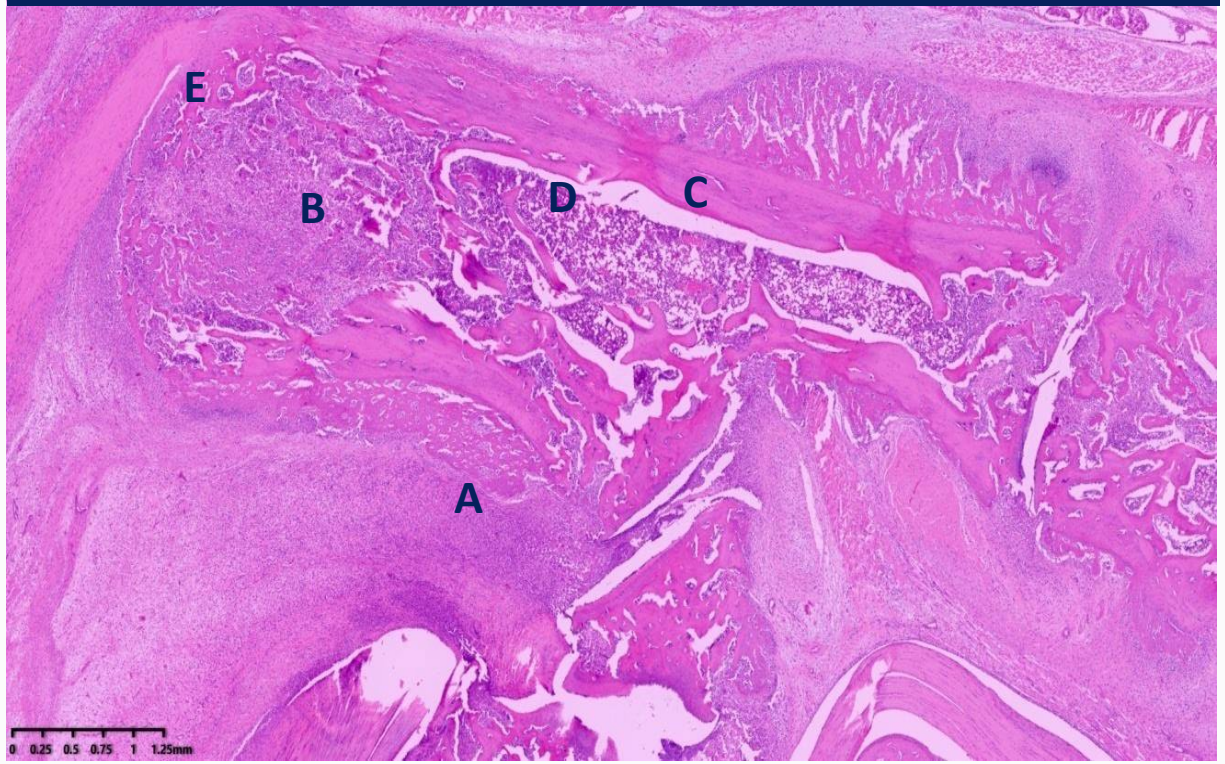
Note: Histology - Mixed cell inflammation; tissue granulation; increased bone, periosteum; increased eroded surface bone and cartilaginous erosion/ulceration were assessed on a 4-point severity scale: minimal (1), mild (2), moderate (3) and marked(4). Composite histopathology score was calculated by summing each assessment by severity and incidence. Maximum score: 160 (5 x 4 x N=8/group).

VYNE™ THERAPEUTICS

VYN202: Collagen-Induced Arthritis Rat Model – Pathology Images

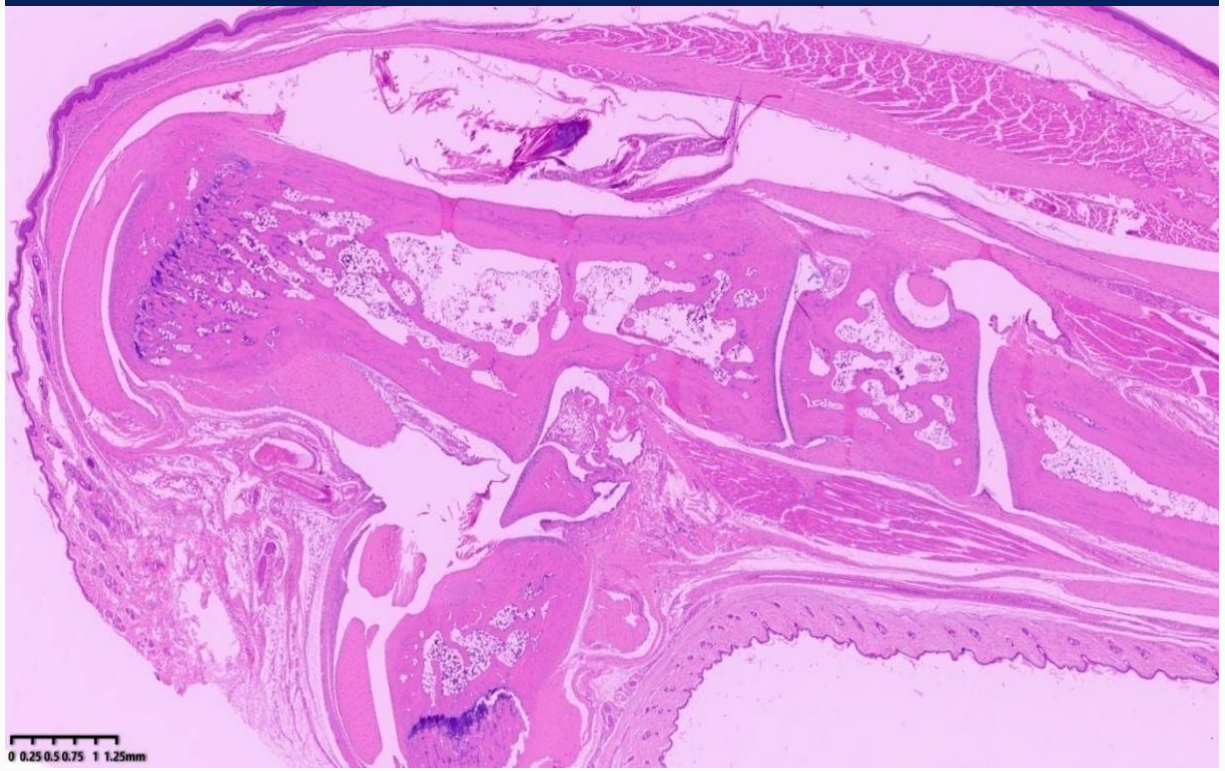
Treatment with VYN202 at 10mg/kg PO QD results in near normal joint pathology

CIA+Placebo



A. Inflammation; mixed cell, marked
B. Granulation tissue; marked
C. Increased bone, periosteum; marked
D. Increased eroded surface, bone; moderate
E. Erosion/ulcer; cartilagenous, moderate

CIA+VYN202 10mg/kg

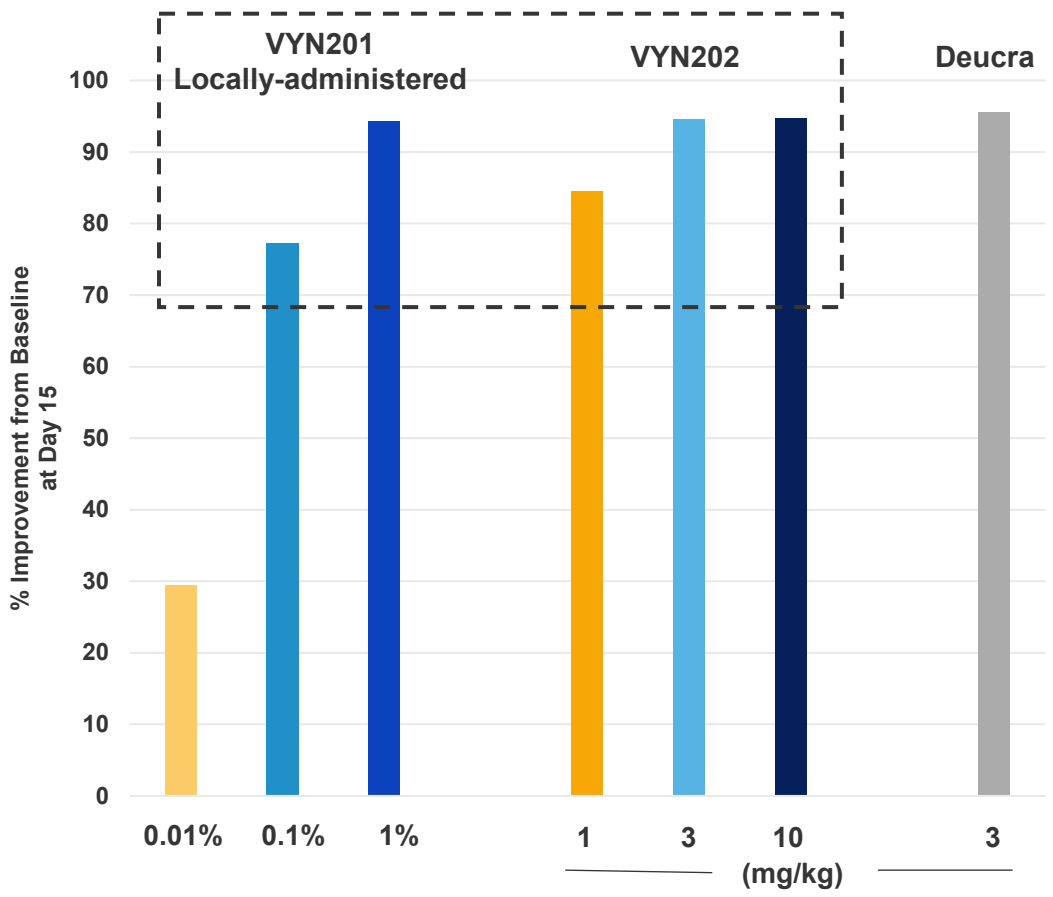


- Normal joint presentation

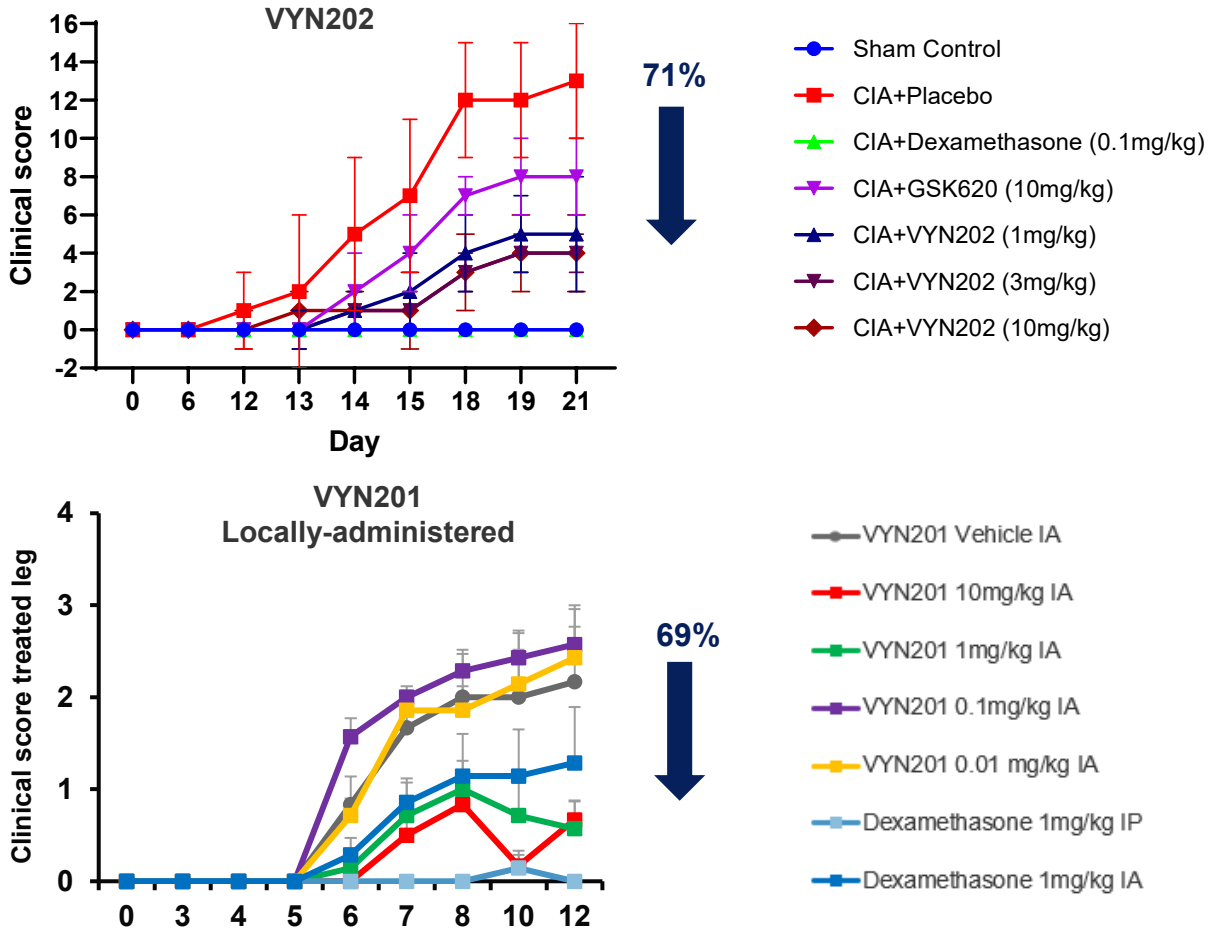
VYN202 Results Show Strong Correlation with VYN201 Results

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

Psoriasis Model



Arthritis Model



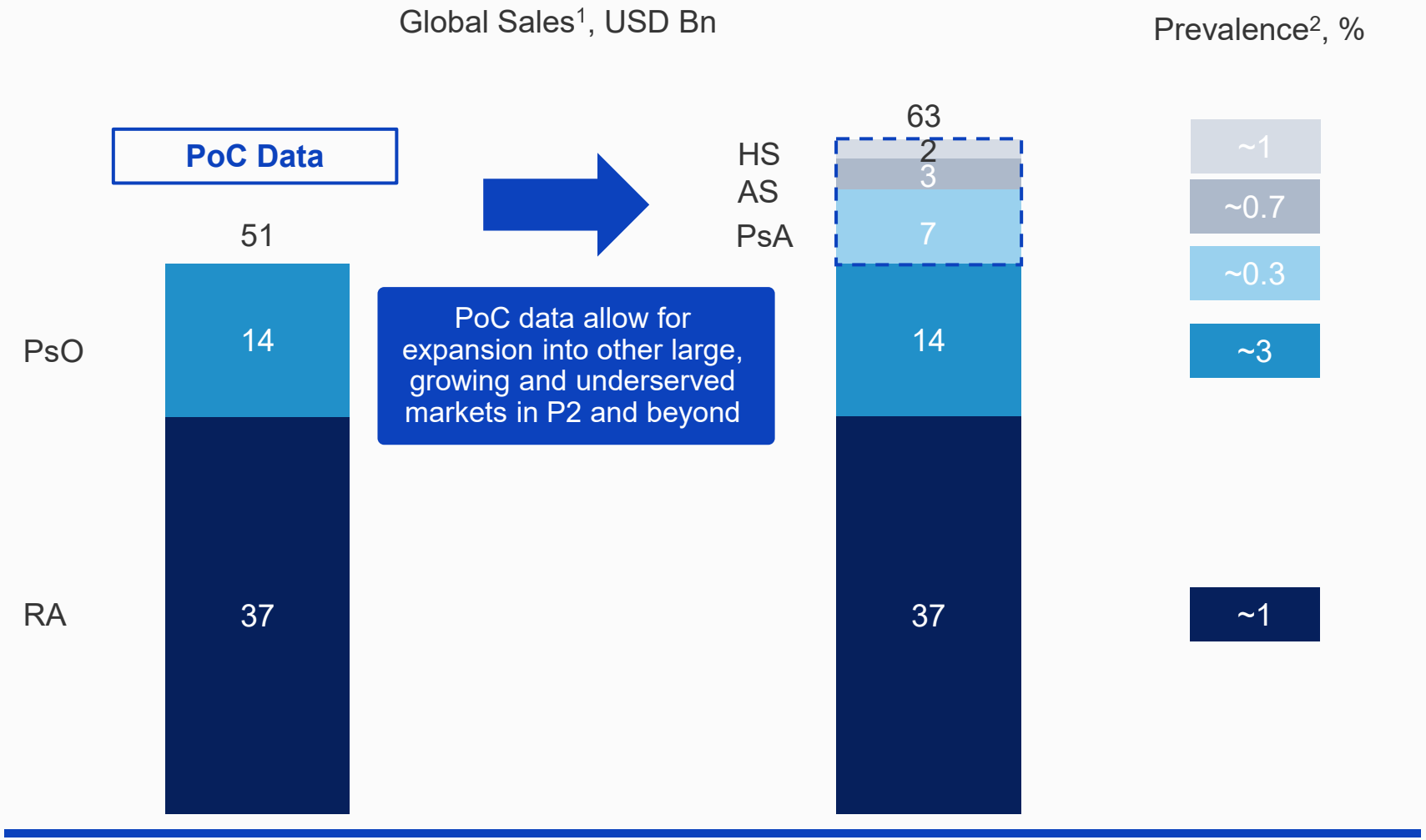
VYN202 Clinical Development Plan

1. Moderate-to-Severe Psoriasis
2. Moderate-to-Severe Active Rheumatoid Arthritis

VYNE™ THERAPEUTICS

Clinical Development Strategy

Initial PoC studies in psoriasis and rheumatoid arthritis serve as potential gateway to other large, strategically attractive markets



VYN202's impact on multiple inflammatory pathways unlocks potential for broad development strategy across range of immune-mediated diseases

Based on MOA and preclinical data, additional opportunities in other disease areas across:

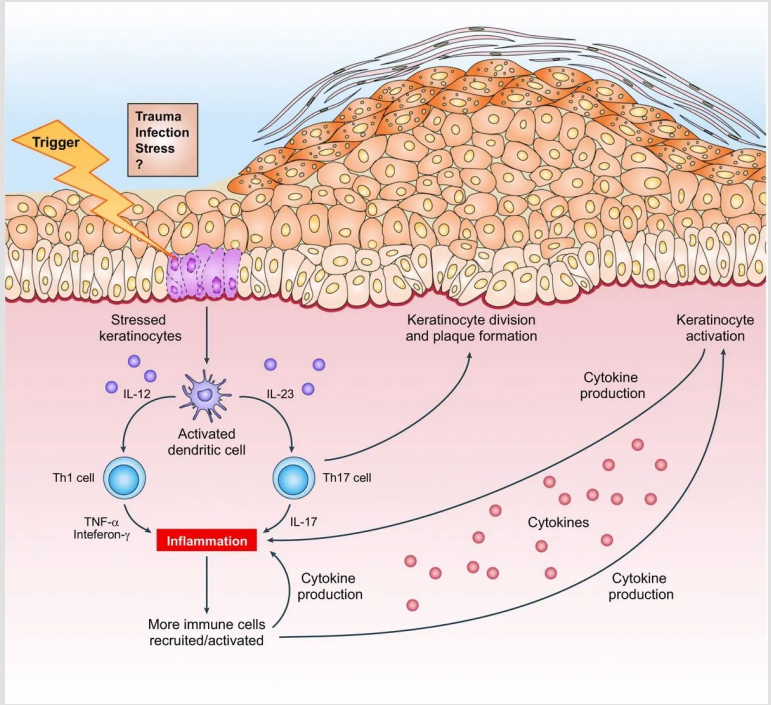
- Dermatology
- Rheumatology
- GI
- Pulmonology and
- Oncology

Source: 1. Global Data; ABBV 2020 Long-term Strategy Corporate Presentation; Data on file 2. Alotaibi HM Clin Cosmet Investig Dermatol. 2023; MacGearailt C., Fitzgerald, G. EMJ Rheumatol. 2021; Ogdie A, Weiss P. Rheum Dis Clin North Am. 2015; Armstrong, et al. JAMA Dermatol. 2021; RA Xu Y, Wu Q. J Clin Med. 2021

Psoriasis: Rationale and Preclinical Proof-of-Concept

Pathogenesis

Fig 1: Mechanism of Psoriasis underscores the importance of regulation of multiple inflammatory pathways[1]



Regulation of inflammatory networks via BET inhibition can reduce IL-17, IL-12/23, TNF-α production and attenuate aberrant inflammatory signaling in psoriasis

Proof of Concept / Rationale

- Aberrant expansion of proinflammatory Th17 cytokines like **TNF-α, IL-12, and IL-23** is linked to BET activity and has been **associated with psoriasis**[2, 3]
- Recent studies have shown that **BET inhibition inhibits proliferation and promoted apoptosis** of psoriatic keratinocytes via **suppression of the MAPK/NF-kB signaling pathway**[4]
- *In vitro* studies with VYN202 show that **VYN202 markedly inhibits the release of IL-17 and IL-22 in Th17–stimulated human peripheral blood mononuclear cells (PBMCs)**
- *In vivo* studies show **VYN201 (topical) and VYN202 reduce IL-17, IL-6, IL-22, IL-23 and TNF-α release** compared to control in psoriatic models and **VYN202 has a comparable inhibitory effect compared to TYK2 inhibitor deucravacitinib, approved for psoriasis**

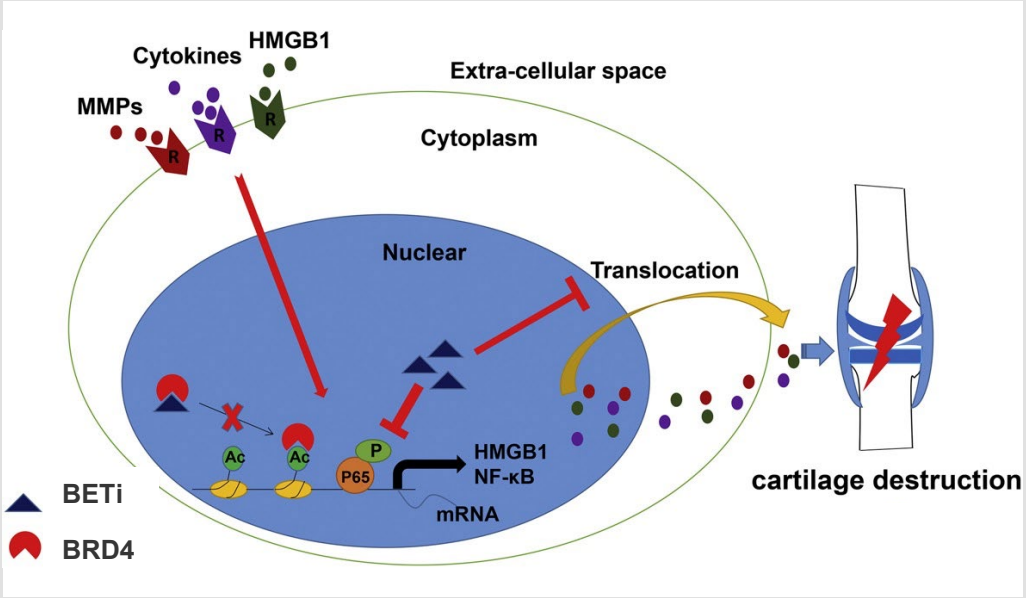
Clinical PoC data provide significant optionality and is a potential gateway to P2 opportunities in indications such as PsA, AS and HS, among others

Sources: Young M et al. JAANP. 2017; 2: Ben Abdallah H et, al. Psoriasis (Auckl). 2021; 3: Sugaya M. Int J Mol Sci. 2020; 4:Sun, X., Yang, P. BioMed Eng OnLine. 2021

Rheumatoid Arthritis: Rationale and Preclinical Proof-of-Concept

Pathogenesis

BET proteins have dual effects on HMGB1 and NF-kB signaling pathways, both of which play critical roles in the pathogenesis of RA



Adapted from Yafei J. *et al, BBA – Molecular Basis of Disease*, 2017

BET inhibition can downregulate HMGB1 and NF-kB pro-inflammatory pathways and reduce levels of inflammatory cytokines with anti-RA effects

Proof of Concept / Rationale

- BET proteins play a role in the mitigation of pro-inflammatory pathways, including **HMGB1** and **NF-kB**, in arthritic diseases[1-2]
- **BET inhibition** has been shown to **block NF-kB signaling pathway activation with anti-RA effects** *in vitro* and *in vivo*[1] and **reduce NF-kB-mediated inflammatory cytokines IL-1β, IL-6, IL-17, and IL-18**[3]
- *In vivo* arthritis studies using **VYN201 (intra-articular injection) and VYN202 showed marked reduction in arthritic clinical signs and symptoms, arthritic histopathology** and **near complete inhibition of IgG expression**
- **VYN202** has **demonstrated superior anti-inflammatory effect** on clinical signs and symptoms **compared to a BD2-selective BET inhibitor from GSK (GSK620)**
- **Treatment with VYN202 showed >98% suppression of** the inflammatory biomarker, **IgG1 with majority of animals being histologically clear of arthritis** at the highest dose

Large commercial opportunity in RA alone and PoC data allow for potential expansion into other arthritic indications

Sources: 1. Yafei J. et al, BBA – Molecular Basis of Disease, 2017; 2. Yuanji, D. et al. Frontiers in Immunology. 2022; 3. Zhang QG, Qian J, Zhu YC. Immunol Lett. 2015

VYN202 Planned Study Designs

Healthy Volunteers

SAD → MAD

Placebo-controlled study evaluating safety, tolerability, PK and PD

SAD

- Trial size: N=~40
  Evaluating 5 strengths of VYN202 (N=8 / cohort) and food effect
- MRSD to be determined based on final IND-enabling non-clinical safety program

MAD

- Trial size: N=~24
  Evaluating 3 strengths of VYN202 once-daily for 14 days (N=8 / cohort)
- Strengths evaluated to be determined by SAD results
- Measurement of key biomarkers (HEXIM-1, TGFβ-1, IL-1β, IL-17, TNFα)

P1 SAD/MAD expected to be initiated in early 2024 with results anticipated in mid-2024

PoC Studies in Patients with Disease

Psoriasis (Mod/Severe)

- Multicenter, double-blind, placebo-controlled phase 1b study
- Trial size: N=~40
  3:1 randomization to treatment with oral VYN202 capsules (low dose, high dose) or placebo once daily in two ascending cohorts
- Duration: 12 weeks
- Entry criteria: Subjects aged 18+ with a clinical diagnosis of moderate-to-severe plaque psoriasis (IGA≥3, PASI≥12).
- Safety/tolerability, PK, PD biomarkers, exploratory efficacy (%CFB PASI, Proportion of subjects ≥PASI50, 75 and 90)

Rheumatoid Arthritis (Mod/Severe)

- Multicenter, double-blind, placebo-controlled phase 1b study
- Trial size: N=~40
  3:1 randomization to treatment with oral VYN202 capsules + MTX (low dose, high dose) or placebo + MTX once daily in two ascending cohorts
- Duration: 12 weeks
- Entry criteria: Subjects aged 18+ with a clinical diagnosis of adult-onset moderate-to-severe active rheumatoid arthritis (≥4 target joints, DAS28-CRP ≥3, hsCRP≥5µg/ml) on a stable dose of MTX for 90 days.
- Safety/tolerability, PK, PD biomarkers, exploratory efficacy (DAS28-CRP and ACR20/50/70 and %CFB in hsCRP.

PoC studies expected to be initiated in 2H 2024 with TLR anticipated in mid-2025

PoC data in PsO and RA provide significant optionality and unlock potential opportunities in other indications such as PsA, AS and HS in P2 and beyond

Current estimate; Subject to clearance of IND by the FDA

VYN202 Program Summary

- Novel, highly differentiated MOA - acting at the point of gene transcription in T Cells to directly address the complex signaling of immuno- & fibro-inflammatory diseases
- BET Inhibition's impact on multiple inflammatory pathways unlocks potential across broad range of immune-mediated diseases

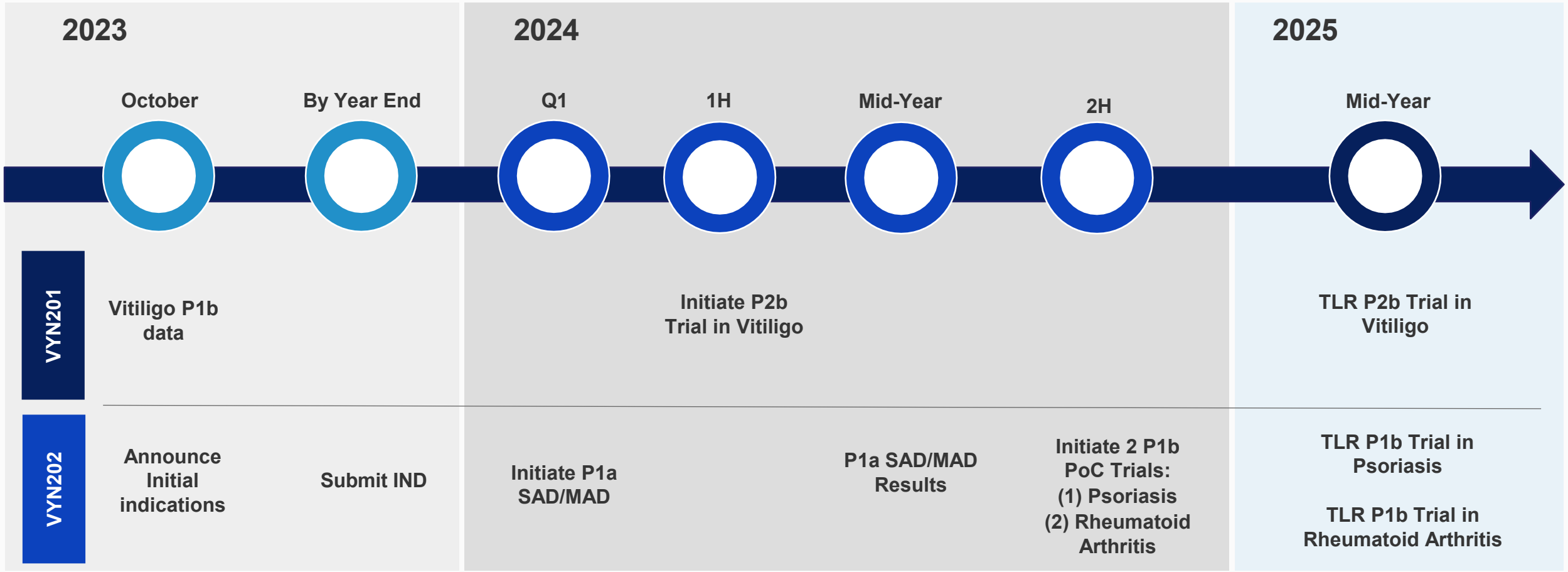
- Historical pan-BD BET safety concerns addressed via potential class-leading selectivity and potency vs. BD2 binding domain and supported by completed and on-going nonclinical toxicity studies

- Strong preclinical data across multiple diverse models of autoimmune disease demonstrating significant down regulation of key pro-inflammatory & disease-related biomarkers with corresponding improvements in disease severity

- VYN202 preclinical efficacy results show strong correlation with VYN201 results reinforcing drug design thesis and BET inhibition potential in psoriasis, rheumatoid arthritis, and other TH17 driven diseases

VYNE™ THERAPEUTICS

Multiple Paths to Potential Value Creation Across BET Inhibitor Programs



Cash runway through the end of 2025

Based on current estimates.

NASDAQ: VYNE