VYNE™ THERAPEUTICS

INVESTOR PRESENTATION

March 2023

ROOTED IN INNOVATION

Forward Looking Statements

This presentation includes forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 including, but not limited to, statements regarding preclinical and clinical development and timelines for VYNE's BET inhibitor platform, VYNE's intention to exercise its option for VYN202 and initiate IND-enabling studies, VYNE's ability to fund its operations into the fourth quarter of 2023, and other statements regarding the future expectations, plans and prospects of VYNE. All statements in this presentation which are not historical facts are forward-looking statements. Any forward-looking statements are based on VYNE's current knowledge and its present beliefs and expectations regarding possible future events and are subject to risks, uncertainties and assumptions that could cause actual results to differ materially and adversely from those set forth or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to: VYNE's ability to successfully develop its product candidates; the timing of commencement of future preclinical studies and clinical trials and the receipt of results in such studies and trials; VYNE's ability to enroll patients and successfully progress, complete, and receive favorable results in, clinical trials for its product candidates; VYNE's ability to exercise its exclusive option with respect to oral BETi candidates pursuant to the terms of the option agreement with Tay Therapeutics Limited (formerly In4Derm Limited); VYNE's intentions and its ability to obtain additional funding, either through equity or debt financing transactions or collaboration arrangements; disruptions related to COVID-19 or another pandemic, epidemic or outbreak of a contagious disease, on the ability of VYNE's suppliers to manufacture and provide materials for VYNE's product candidates, initiating and retaining patients in clinical trials, operating results, liquidity and financial condition; the regulatory approval process for VYNE's product candidates, including any delay or failure in obtaining requisite approvals; the potential market size of treatments for any diseases and market adoption of products, if approved or cleared for commercial use, by physicians and patients; developments and projections relating to competitors and the pharmaceuticals industry, including competing drugs and therapies; the timing or likelihood of regulatory filings and approvals or clearances for product candidates; VYNE's ability to comply with various regulations applicable to its business; VYNE's ability to create intellectual property and the scope of protection it is able to establish and maintain for intellectual property rights covering its product candidates, including the projected terms of patent protection; risks that any of VYNE's patents may be held to be narrowed, invalid or unenforceable or one or more of VYNE's patent applications may not be granted and potential competitors may also seek to design around VYNE's granted patents or patent applications; the timing, costs or results of litigation, including litigation to protect its intellectual property; VYNE's ability to successfully challenge intellectual property claimed by others; estimates of VYNE's cash runway, expenses, capital requirements, its needs for additional financing and its ability to obtain additional capital on acceptable terms or at all; VYNE's ability to attract and retain key scientific or management personnel; VYNE's defense of any litigation that may be initiated against it; VYNE's expectations regarding licensing, business transactions and strategic operations; VYNE's future financial performance and liquidity; and volatility in VYNE's stock price may result in rapid and substantial increases or decreases in the stock price that may or may not be related to the company's operating performance or prospects. For a discussion of other risks and uncertainties, and other important factors, any of which could cause VYNE's actual results to differ from those contained in the forward-looking statements, see the section titled "Risk Factors" in VYNE's Annual Report on Form 10-K for the year ended December 31, 2021 and Quarterly Report on Form 10-Q for the period ended September 30, 2022, as well as discussions of potential risks, uncertainties, and other important factors in VYNE's subsequent filings with the U.S. Securities and Exchange Commission. Although VYNE believes these forward-looking statements are reasonable, they speak only as of the date of this presentation and VYNE undertakes no obligation to update publicly such forward-looking statements to reflect subsequent events or circumstances, except as otherwise required by law. Given these risks and uncertainties, you should not rely upon forward-looking statements as predictions of future events.

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

Multiple paths to potential value creation and catalysts

Program	Potential Indication(s)	Route of Administration	Current Stage				Anticipated Milestones & Recent Updates	Rights
			Preclinical	Phase 1	Phase 2	Phase 3		
InhiBET™ Platform								
VYN201 "Soft" pan-BD BET inhibitor	Nonsegmental Vitiligo[1]	Topical					• Phase 1a completed • Mid-2023: Phase 1b TLR in vitiligo patients	Worldwide
	Those benefiting from local administration, "soft drug" approach, and anti-fibrotic activity such as rheumatology and lung disease	Inhaled / Injectable					• 2023: Selection of 2nd indication	Worldwide
VYN202 BD2-selective BET inhibitor	I&I such as RA, systemic lupus erythematosus, UC/Crohn's and MS[1]	Oral					• Exercise of option • 2023: Selection of indication • 2023: Submit IND	Worldwide
Exclusive Access to Library of NCE BET Inhibitors for Any Indication Worldwide								
FMX114 JAK inhibitor / S1P receptor modulator	Atopic Dermatitis (AD)	Topical					• Phase 1b/2a Complete • Phase 2b ready	Worldwide

Note: Cash runway guidance into Q4 2023 assumes development activities for VYN201 in nonsegmental vitiligo and continued advancement of VYN202, based on current estimates. Refer to slide 2 "Forward Looking Statements" for description of risks and uncertainties regarding the future expectations, plans and prospects of VYNE. Subject to adequate levels of funding.

1. List included is illustrative and not exhaustive and subject to exercise of option and completion of requisite pre-clinical evaluations. VYNE currently anticipates exercising its exclusive option with respect to VYN202 prior to its expiration on April 30, 2023

BET = Bromodomain and extra-terminal protein
FPI = First Patient In/Enrolled
TLR = Top Line Results

InhiBET™ BET Inhibitor Platform

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

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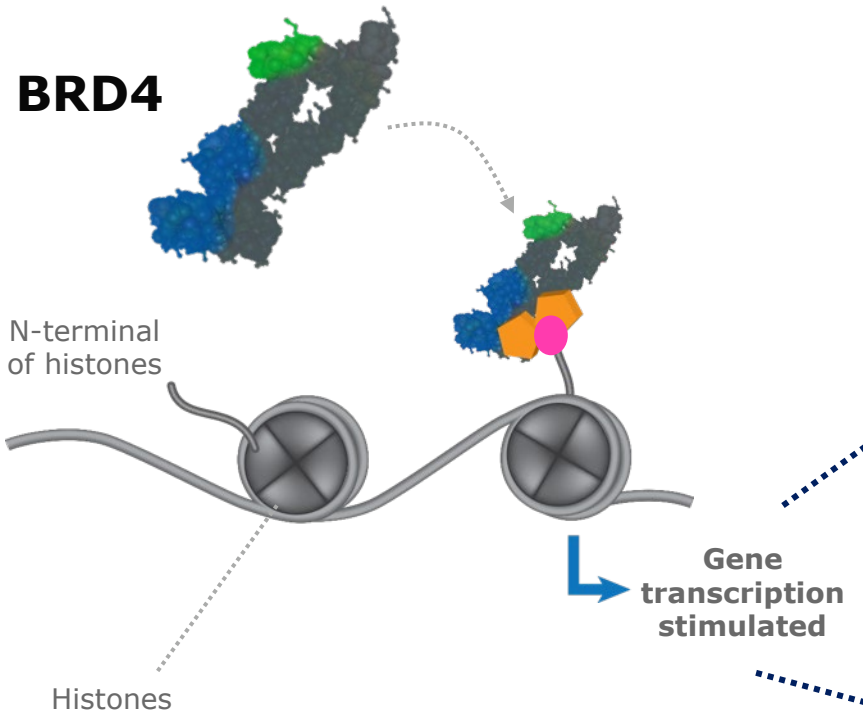
BET Proteins Play a Key Role
in the Regulation of Inflammatory and Oncogenic Genes involved in Several Diseases



BET proteins "read" acetylated lysines and enable transcription of:

Pro-inflammatory genes, leading to:
- Increased cytokine expression that activate B&T cells
- An increase in autoimmune and cardiovascular diseases

Oncogenic genes, leading to:
- Increased cell proliferation/survival
- An increase in solid tumors and hematologic malignancies

BD1 and BD2 Domains of BET Protein are Recognized as Druggable Targets

and BET Inhibition Represents a Differentiated Approach to Treating Autoimmune Diseases

BRD4 BET Protein

- BET proteins are characterized by 2 bromodomains (BD1 and BD2) and 1 extra-terminal domain
- BD1 and BD2 enable chromatin remodeling and recruit transcription factors to facilitate gene transcriptions
- Inhibiting BET proteins prevents the formation of complexes required to facilitate transcription, thereby inhibiting the subsequent translation of a corresponding protein
- This targeting is differentiated from drugs that inhibit a specific receptor (e.g., blocking the active site of tyrosine kinases such as JAKs)
- BET inhibitors have been shown to have a marked impact on reducing cytokine expression in several models of autoimmune disease

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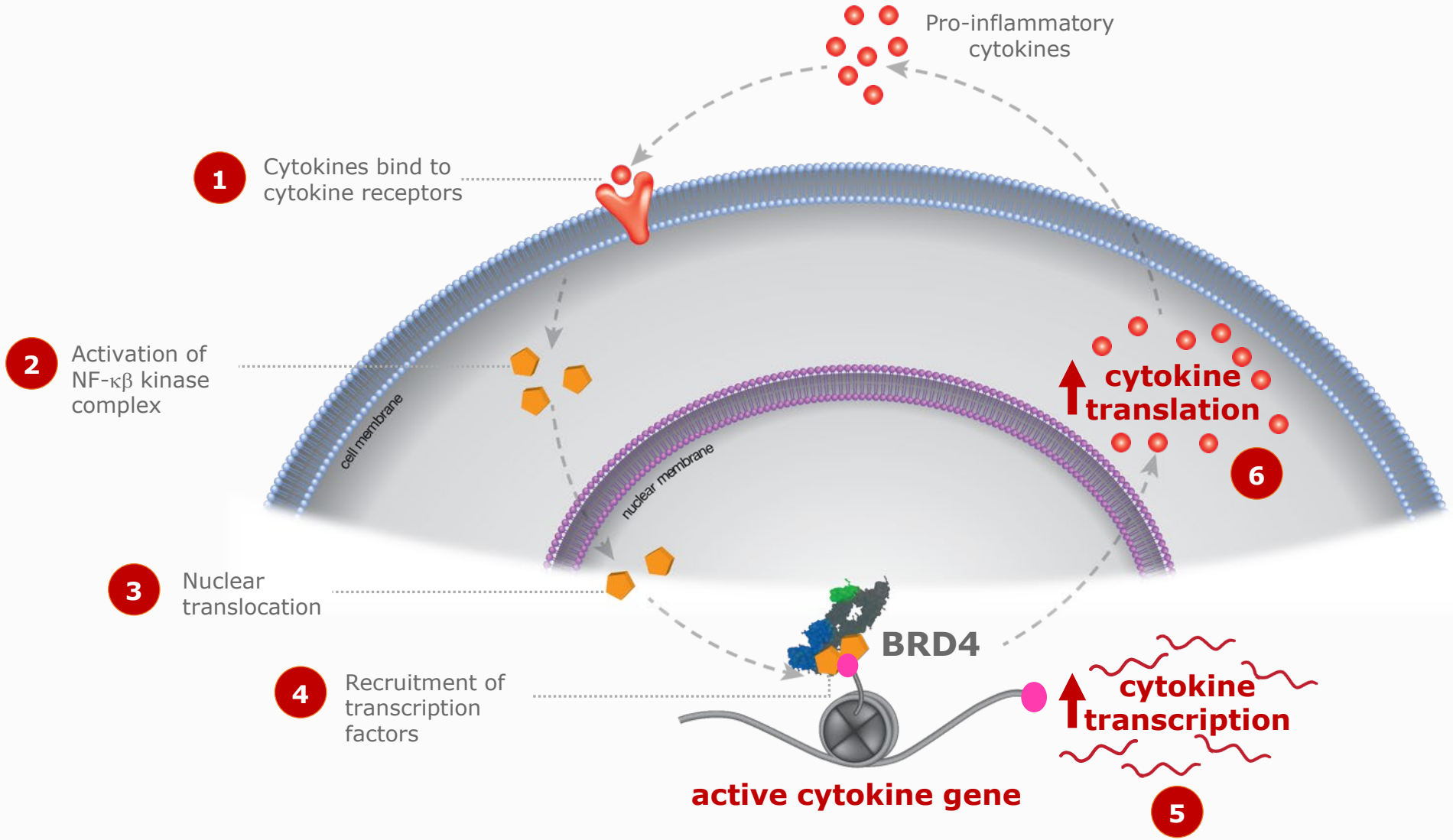
Shi & Vakoc, *Mol. Cell* 2014

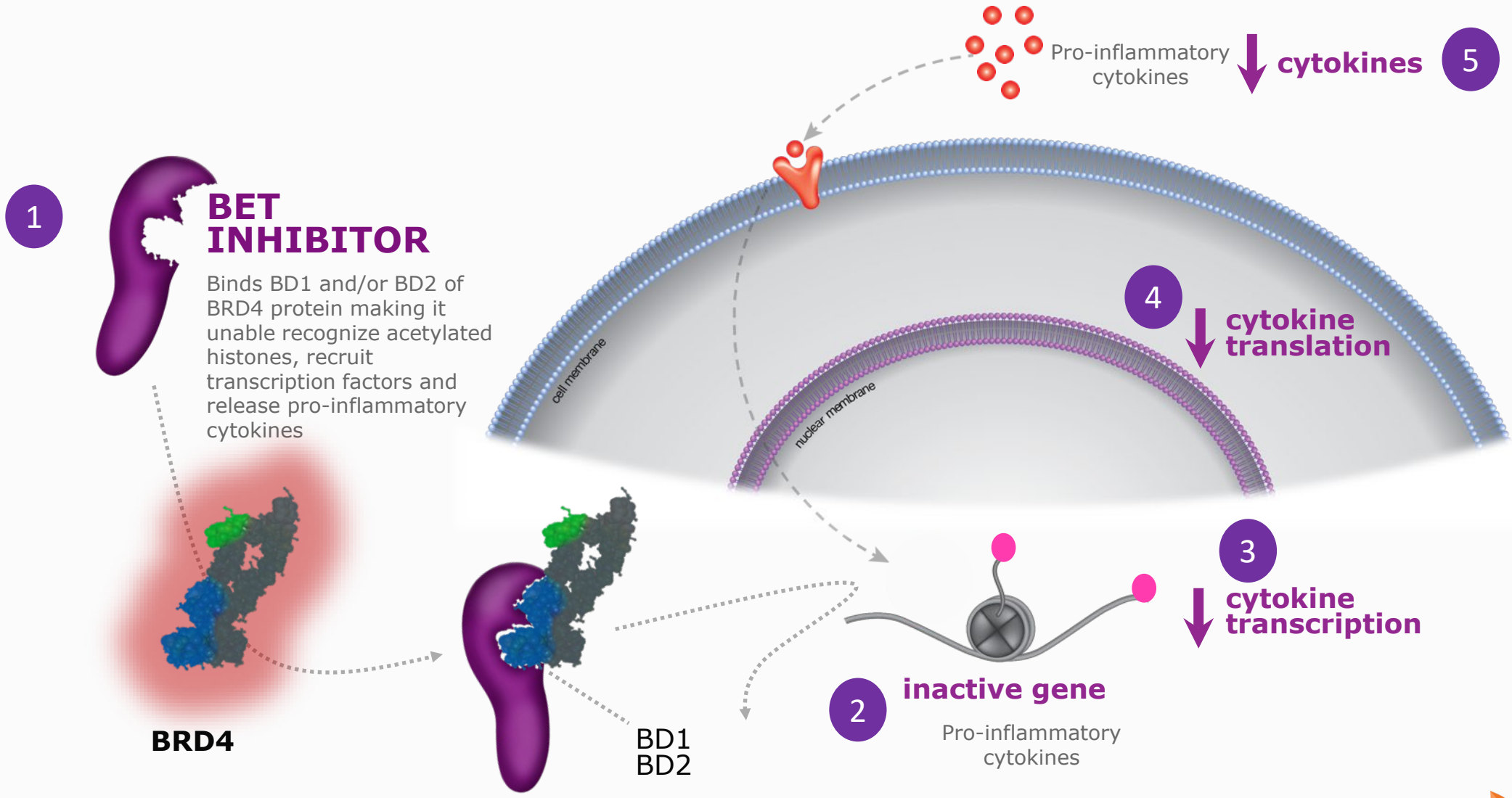
How BET Proteins Fuel the "Vicious Cycle"
of Pro-Inflammatory Cytokine Production in Autoimmune Diseases



NF-κB = Nuclear Factor Kappa B

BET Inhibitors Block BD1/BD2 Binding

to Acetylated Lysines and Stall Pro-inflammatory Protein Transcription



BD1 and BD2 Play Different Roles in Regulating Gene Expression

Maximizing on-target potency against BD2 and minimizing affinity to BD1 may be the key to optimizing the benefit/risk profile of BET inhibitors for autoimmune diseases

BD1 and BD2 role differentiation:

Characteristic	BD1	BD2
Key to steady-state gene regulation?	Yes	No
Key to inflammatory gene induction?	No	Yes
Anti-inflammatory effect via selective antagonism?	No	Yes
GI and hematological toxicities via selective antagonism?	Yes	No

- BD1 regulates "housekeeping" gene activity. BD1 inhibition via systemic administration has been linked to potential clinical safety findings including GI toxicity and thrombocytopenia
- BD2 BET activity is associated with inflammatory gene induction that drives inflammatory responses in autoimmune disease

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

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VYNE's Drug Design Strategy

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

Pan-BD BET Inhibitors

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

BD2-Selective BET Inhibitors

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
Locally administered pan-BET inhibitor

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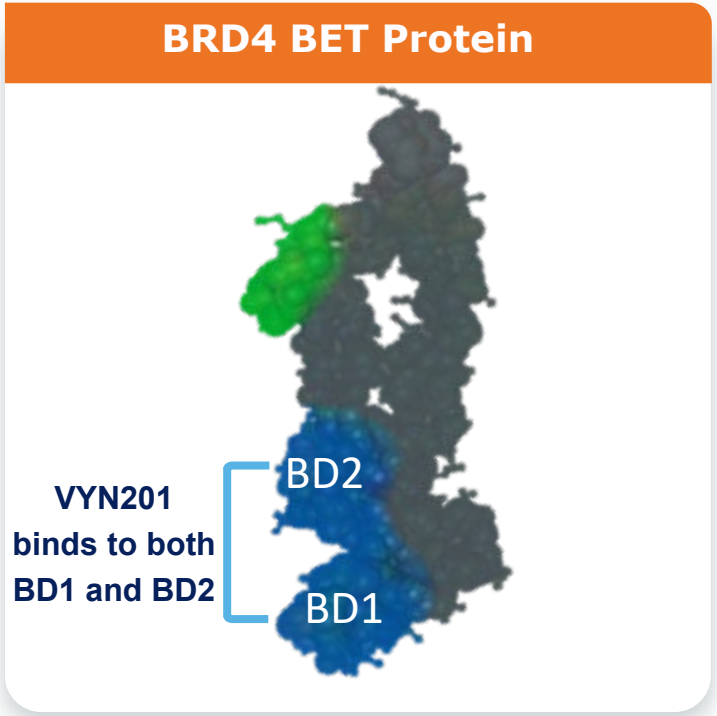
VYN201 – Locally Administered Pan-BD BET Inhibitor

Designed as a "soft" drug for tissue targeted administration to maximize local effect and minimize systemic exposure



Potential Target Market:

- Vitiligo
- Other indications benefiting from local administration and "soft drug" approach

Broad activity:

- Binds to BD1 and BD2 domains (pan-BD)

Targeted Near Term Milestones:

- Mid-2023: VYN201 Phase 1b TLR in vitiligo

TLR = Top Line Results

VYN201 Pre-Clinical Efficacy Model Evaluations

Program designed to investigate the targeted administration of a "soft drug" pan-BD BET inhibitor to maximize local effect and minimize systemic exposure

Indication/area	Model	Administration Route	Status
Th17 autoimmune diseases	IMI-induction mouse model	Topical	Complete
Th2 autoimmune diseases	DNCB-induction mouse model	Topical	Complete
Fibrosis	Wound healing outcomes mouse model	Topical	Complete
Vitiligo	Reconstituted human epithelial skin TNFα/IFNγ induction model	Topical	Complete
Idiopathic pulmonary fibrosis	Bleomycin-induction mouse model	Intra-nasal	Complete
Rheumatoid arthritis	Intra-articular cytokine cocktail mouse model	Intra-articular	Complete
Macular degeneration	Choroidal neovascularization rat model	Intra-orbital/vitreous	Complete
Colitis (gut restricted)	DSS-induction mouse model	Oral	Complete
Oncology (AML/melanoma)	Human cell line screening and biomarker discovery	In-vitro	On-going

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VYN201: Preclinical Proof-of-Concept Data Summary

Potential "pipeline in a product" with broad utility across multiple routes of administration

Preclinical models produced consistent reductions in pro-inflammatory & disease-related biomarkers, improvements in disease severity and a demonstrated local activity

Vitiligo Model (Topical)

- Highest doses demonstrated statistically significant improvement in reducing melanocyte loss & lowering key inflammatory biomarkers MMP9 and soluble e-cadherin vs. vehicle
- Numerically superior to active control, ruxolitinib cream, 1.5%

TH17 Inflammation Model (Topical)

- Significantly reduced expression of several key pro-inflammatory proteins relevant to Th17-mediated autoimmune diseases in human tissue
- Reduced composite score of inflammation severity

IPF[1] & Fibrotic Tissue Models (Intra-Nasal and Topical)

- Significantly lower fibrosis vs. vehicle and negative control
- Preliminary IPF model data suggests VYN201 could have promising impact on IPF-related fibrosis and biomarkers

Arthritis Model (Intra-articular Injection)

- Two highest doses produced statistically significant improvement in treatment response
- Demonstrated localized dose-dependent effect

1. Idiopathic pulmonary Fibrosis (IPF)
2. Data on file

VYN201: Vitiligo
Preclinical data and Clinical Plan

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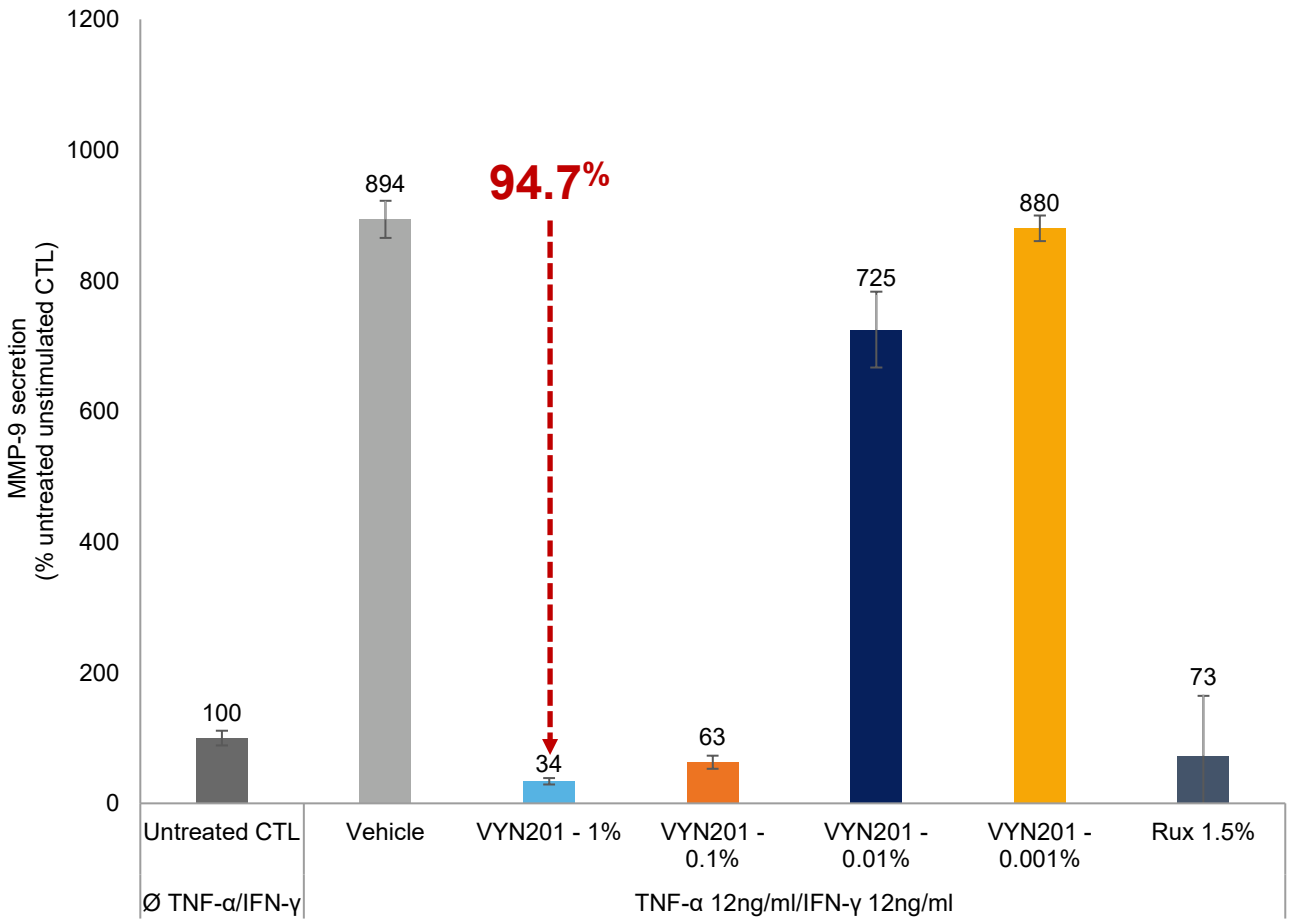
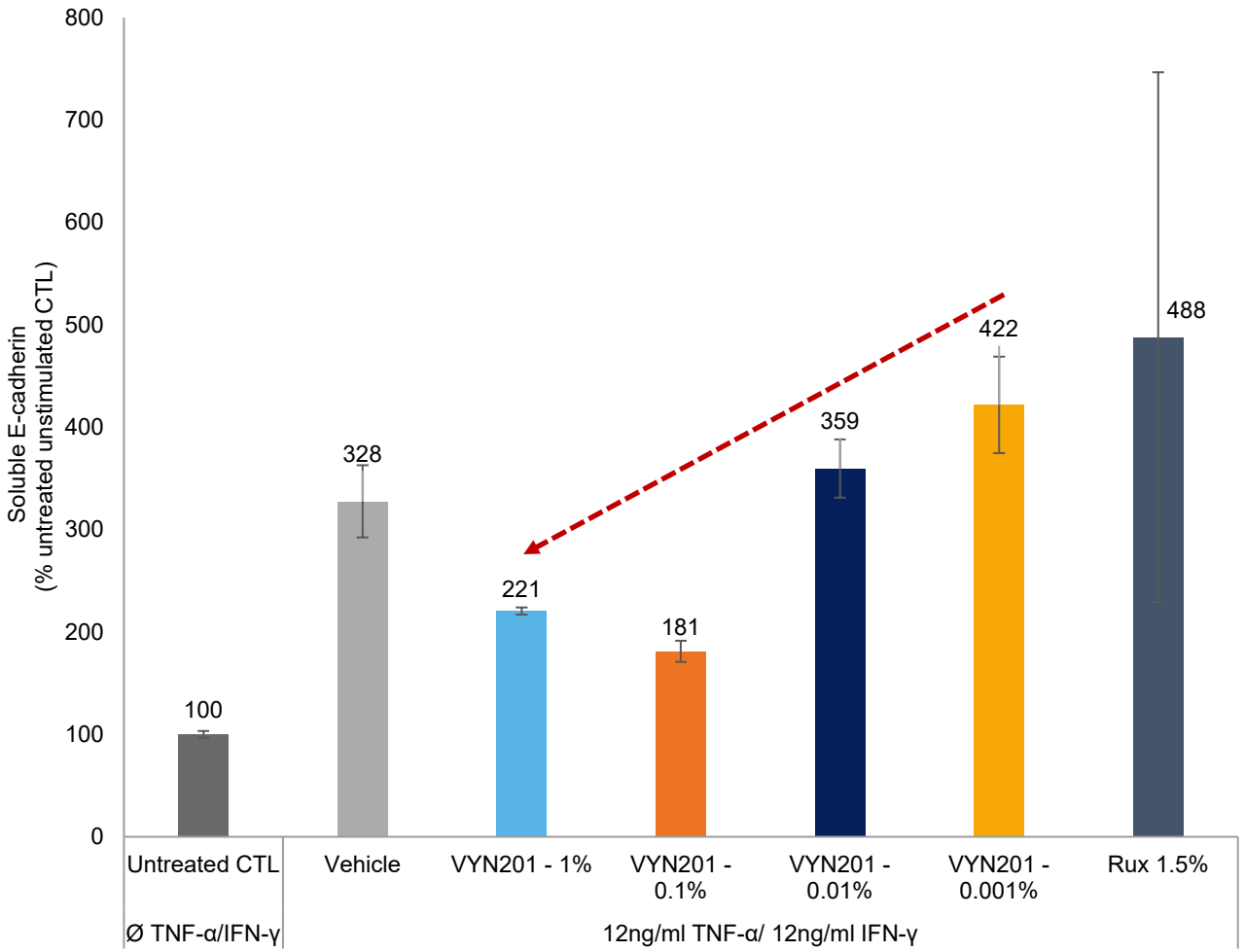
VYN201: Human Tissue Model of Vitiligo – Demonstrated Inhibition of MMP9

Reconstituted human epithelial (RHE) skin cultures were treated with a TNF-α and IFN-γ cytokine cocktail to induce a vitiligo phenotype melanocytorrhagy (loss of melanocyte), upregulation of MMP9 and soluble E-cadherin). 24hr prior to stimulation, RHE samples were topically treatment with VYN201 at varying concentrations and topical ruxolitinib 1.5% cream at 3 mg/cm^2



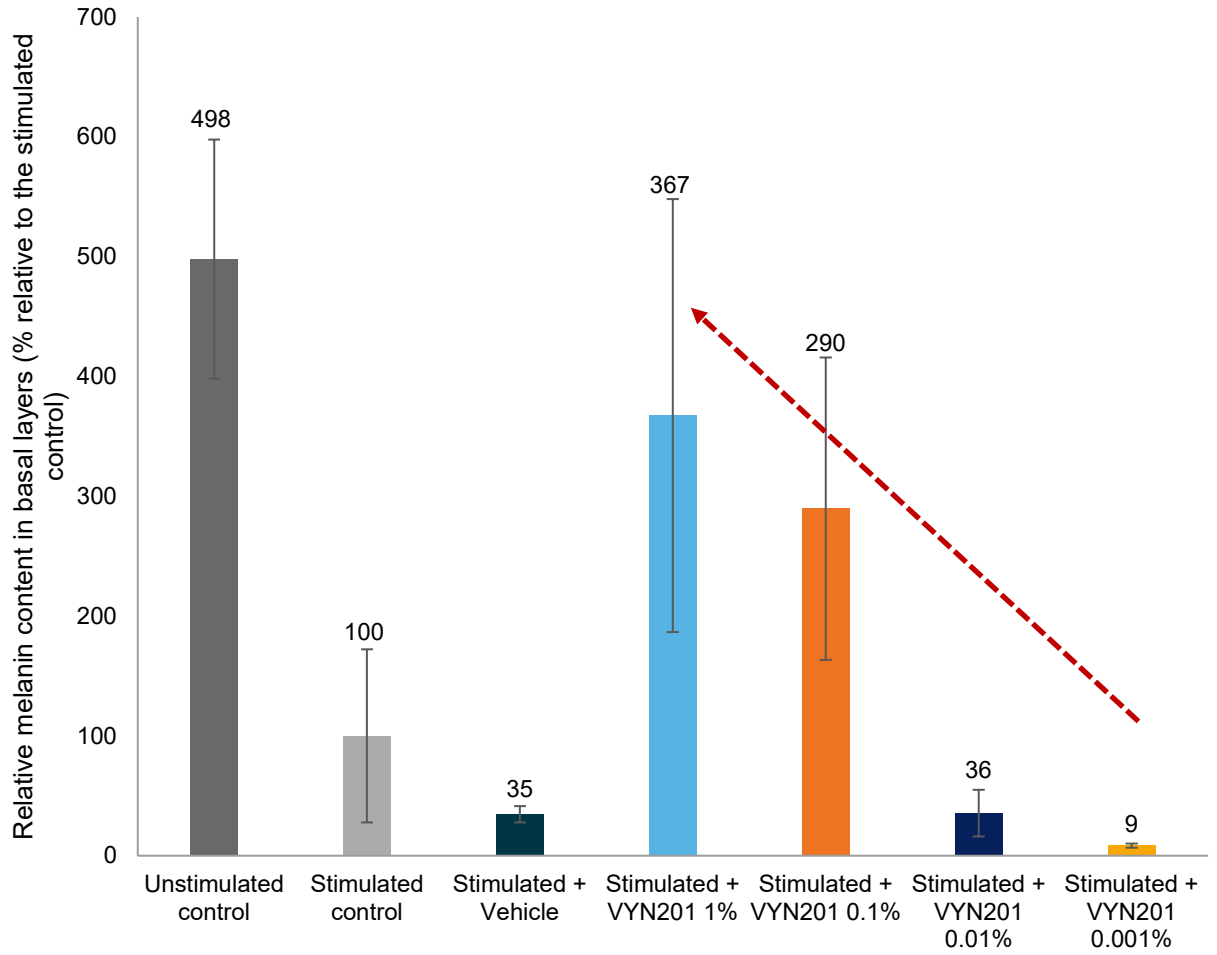
- Stimulated and vehicle treated RHE demonstrated a significant upregulation of MMP9, relative to unstimulated and untreated control
- VYN201 markedly reduced the expression of MMP9 in a dose-dependent manner with a maximal effect at the 1% concentration
- VYN201 1% reduced the secretion of MMP9 by 94.7%, relative to stimulated vehicle, and numerically superior to ruxolitinib 1.5%

VYN201: Human Tissue Model of Vitiligo – Reduction of Soluble E-cadherin



- Stimulated and vehicle-treated RHE demonstrated a significant upregulation of soluble E-cadherin, relative to unstimulated control
- **VYN201 affects a dose-dependent reduction in solubilized E-cadherin**
- VYN201 was numerically superior to topical ruxolitinib cream 1.5%

VYN201: Human Tissue Model of Vitiligo – Effect on Melanocyte Retention

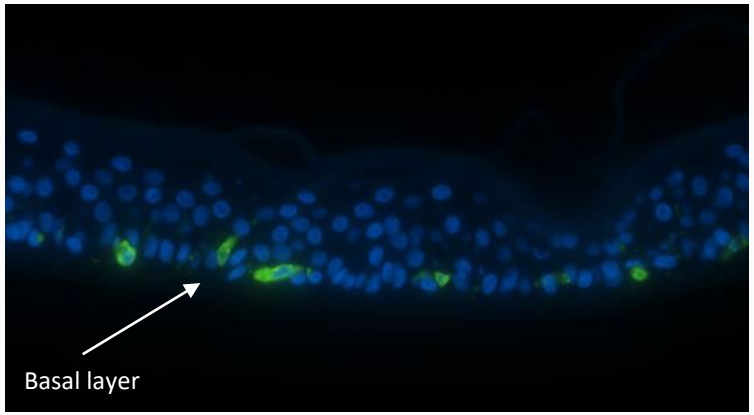


- Stimulated and vehicle-treated RHE demonstrated a significant loss in melanin content, relative to unstimulated control
- **VYN201 substantially prevents the loss of melanin pigment in the basal layers of skin in a dose dependent manner**
- Residual melanin levels for VYN201 1% was approximately 10-fold higher than vehicle, retaining approximately 75% of melanin relative to unstimulated control

Note: Melanin content in skin cultures treated with ruxolitinib 1.5% cream was immeasurable due to tissue intolerance to treatment

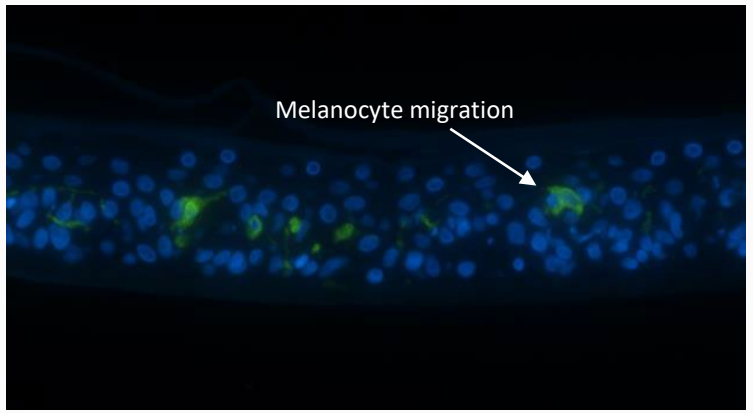
VYN201: Human Tissue Model of Vitiligo - Histology

Micrographic images of TRV immuno-stained induced RHE specimens demonstrating the preservation of melanocytes in the basal layer of samples treated with VYN201 1%



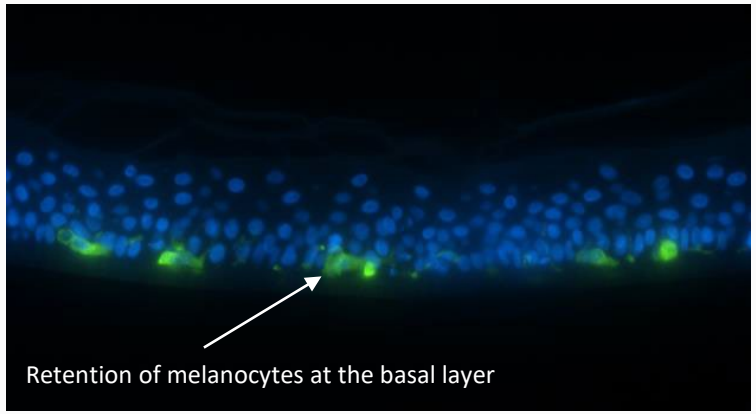
Unstimulated and untreated control

Melanocytes remain at or close to the basal layer implying that E-cadherin adhesion is still functional



Stimulated and Vehicle treated

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



Stimulated and VYN201 1% treated

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

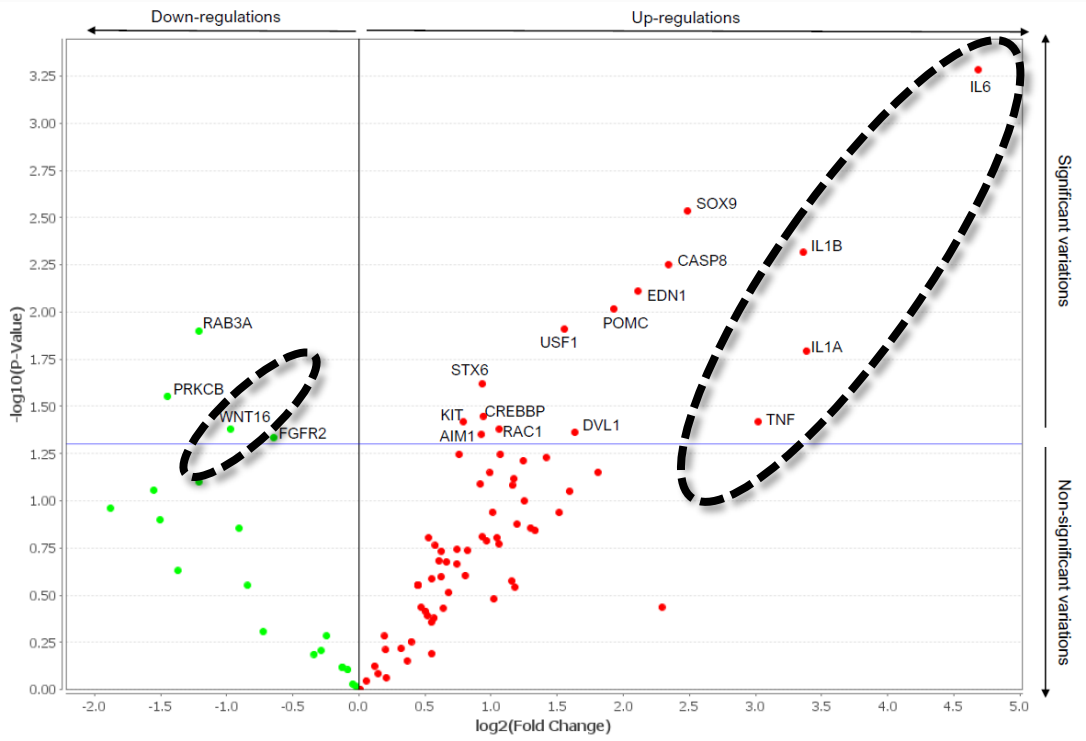
Keratinocytes (blue), melanocytes (green)

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

VYN201: Human Tissue Model of Vitiligo – Gene regulation

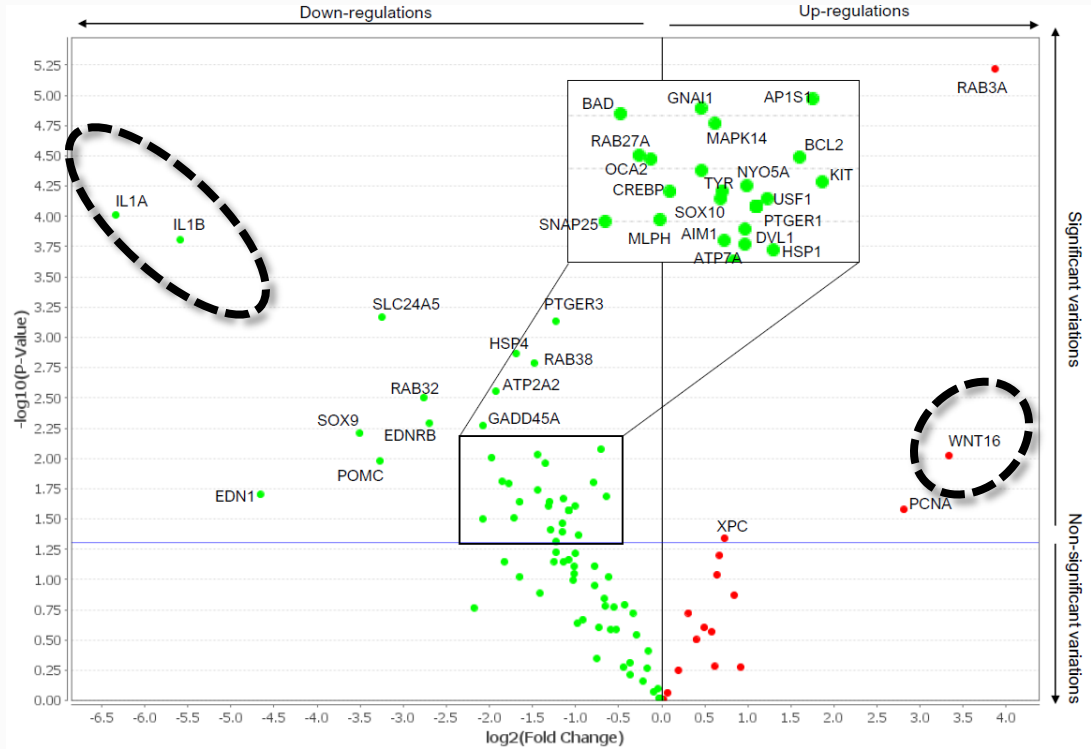
Preliminary data suggest that VYN201 regulates genes relevant to Vitiligo including impacting WNT pathway which is believed to play a key role in melanocyte regeneration

Transcriptome volcano plots of genes relevant to vitiligo (preliminary findings):



Stimulated control

Significant upregulation of cytokines IL6, IL1A and IL1B and TNF



Stimulated and VYN201 1% treated

Significant downregulation of cytokines IL6, IL1A and IL1B and TNF and upregulation of the WNT pathway IL6 and TNF downregulated below LLOQ of assay

LLOQ: Lower Limit Of Quantification

VYN201: Phase 1a/b Study Design in Vitiligo

Topline P1b results anticipated mid-2023

Vitiligo Phase 1a/b design comprising of:

Phase 1a Portion *(Complete)*
(N=30: 5 Cohorts with 6 patients each, evaluating 0.025%, 0.1%, 0.5%, 1.0% and 2.0% strengths)
A single ascending / multiple ascending dose cohort in healthy volunteer participants for up to 2 weeks of once-daily treatment

Primary objective: To identify safe starting doses for vitiligo patients in Phase 1b portion of the study

- Assessments will include TEAEs, pharmacokinetics and local skin tolerance

Phase 1b Portion
(N=30: 3 Cohorts with 10 patients each, evaluating 0.5%, 1.0% and 2.0% strengths)
Treatment on the face and target lesion on trunk of vitiligo patients for up to 16 weeks of once-daily treatment

Primary objective: Evaluation of the safety and pharmacokinetics of VYN201 in vitiligo patients

- Dose level(s) will be selected based on findings from the Phase 1a portion of the study.
- Assessments will include TEAEs, pharmacokinetics, local skin tolerance, efficacy (F-VASI), biomarkers, photography.

TEAE = Treatment Emergent Adverse Events; F-VASI = Facial Vitiligo Area Scoring Index

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VYN201: Phase 1a Topline Safety Results

VYN201 was generally well-tolerated with no clinically relevant TEAEs, meeting the primary objective of the study

Summary of safety and tolerability results (N=30 healthy volunteers)*:

- No SAEs and no dose adjustments were required
- No clinically relevant treatment emergent adverse events, abnormal clinical laboratory results or electrocardiogram findings
- No healthy volunteers withdrew from the trial for any reason
- 0.5%, 1.0% and 2.0% strengths selected for evaluation in the ongoing Phase 1b study evaluating VYN201 in non-segmental vitiligo patients

*N=30 healthy volunteers: 5 Cohorts with 6 patients each, evaluating 0.025%, 0.1%, 0.5%, 1.0% and 2.0% strengths

SAE = Serious Adverse Event; TEAE = Treatment Emergent Adverse Event

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Vitiligo Represents an Exciting Opportunity for VYN201

Positive Phase 1a SAD/MAD study results announced
Phase 1b top-line results anticipated mid-2023

Novel Mechanism of Action with Encouraging Data

- VYN201 utilizes a "soft" drug approach designed to maximize target engagement in the skin and minimize systemic exposure
- VYN201 shown to impact key biomarkers and genes that drive dyspigmentation in vitiligo in validated preclinical human tissue model (TNF-α and IFN-ɣ, MMP9 and E-cadherin)
- Preclinical data suggest that VYN201 regulates WNT pathway which is believed to play a key role in melanocyte regeneration
- Favorable P1a SAD/MAD safety and tolerability data

Significant Unmet Need

- Vitiligo is a disabling disease impacting social, sexual and professional life
- Current treatment dominated by non-specific therapeutics
- Only one FDA-approved Rx drug (JAK) which includes a black box warning

Large Market

- 0.5 to 2.0% of worldwide population
- Non-segmental sub-type represents ~90% of patients
- Est. U.S. prevalence is between 1.9 and 3.2 million cases (diagnosed/undiagnosed)

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

Sources: Bergqvist. Dermatol. 2020;236:571-592; *JAMA Dermatology*, "Prevalence of Vitiligo Among Adults in the United States"; 2022; 158(1):43-50 (published online Nov. 17, 2021); Rangu S, McKenzie PL, Castelo-Soccio L (2021) Therapy Utilization among Children with Vitiligo at an Urban Tertiary Care Center J Clin Dermatol Ther 7: 070.

VYN202: BD2 selective BET inhibitor

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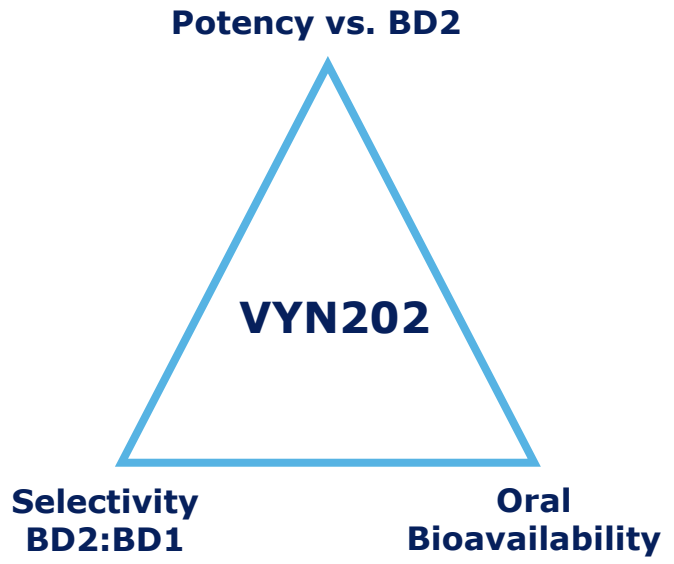
VYN202 – Oral BD2-selective BET inhibitor

Designed with class-leading selectivity (BD2 vs. BD1), targeting improved efficacy and tolerability as compared to other systemic pan-BD BET inhibitors in development

Molecular Profile Design



Potential Target Market[1]:

- Immuno-inflammatory indications such as RA, systemic lupus erythematosus, UC/Crohn's and multiple sclerosis; additional potential in myeloproliferative neoplastic disorders

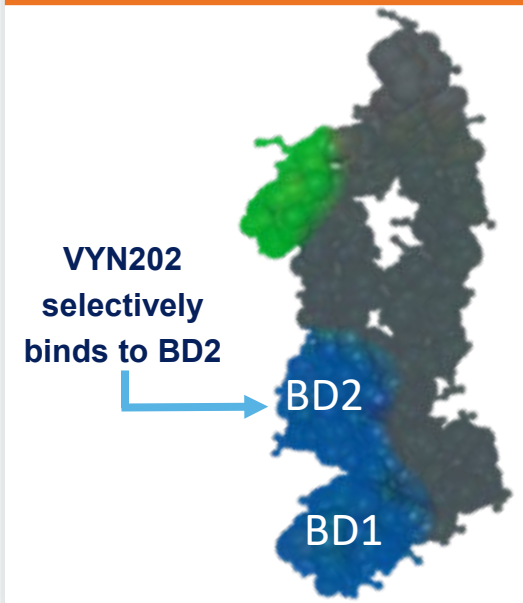
Class Leading Selectivity:

- Highly selective inhibition of BD2 domain of the BRD4 protein
- Targeting improved safety profile compared to oral pan-BD BET inhibitors

Targeted Near Term Milestones:

- 2023: Exercise of option[2], Candidate Selection
- 2023: Submit IND

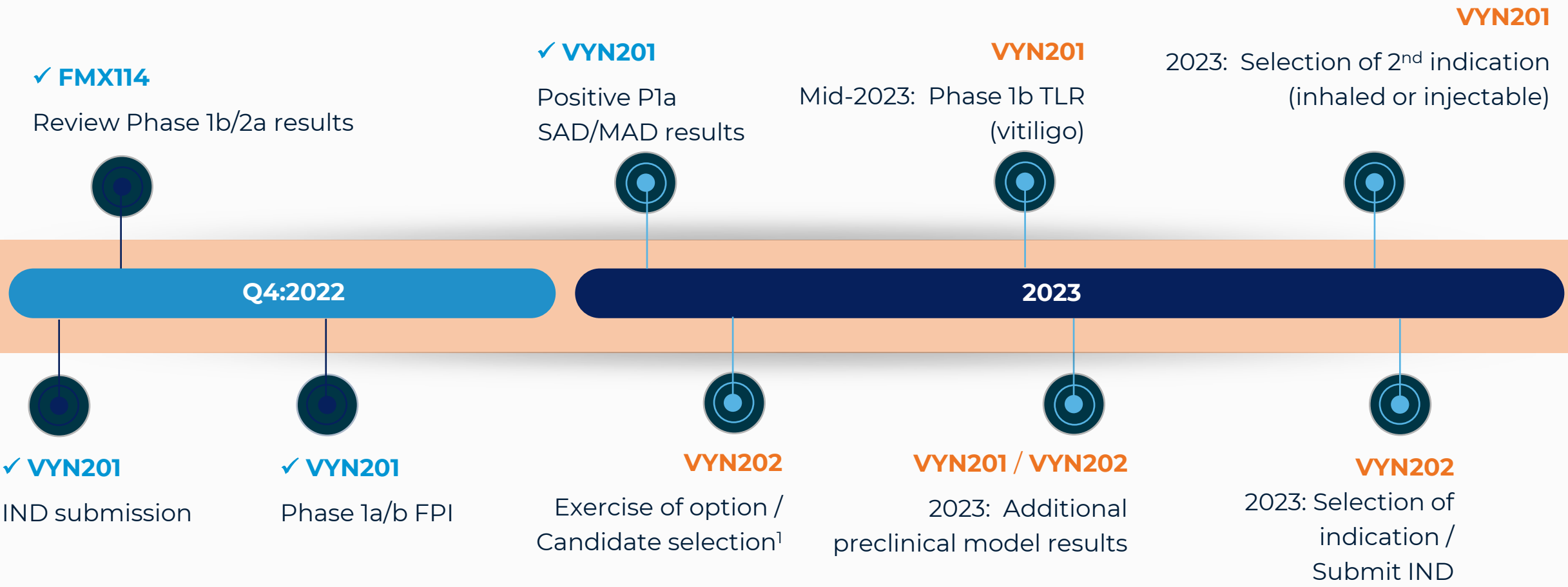
BRD4 BET Protein



1. Initial indication to be communicated following completion of requisite pre-clinical evaluations. List included is not exhaustive of potential indications
2. VYNE currently anticipates exercising its exclusive option with respect to VYN202 prior to its expiration on April 30, 2023

Potential Value-Creating Milestones To Kick-Off 2023

Building a leading early-stage immuno-inflammatory pipeline



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Appendix: VYN201

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VYN201: Vitiligo
Disease / Market Overview

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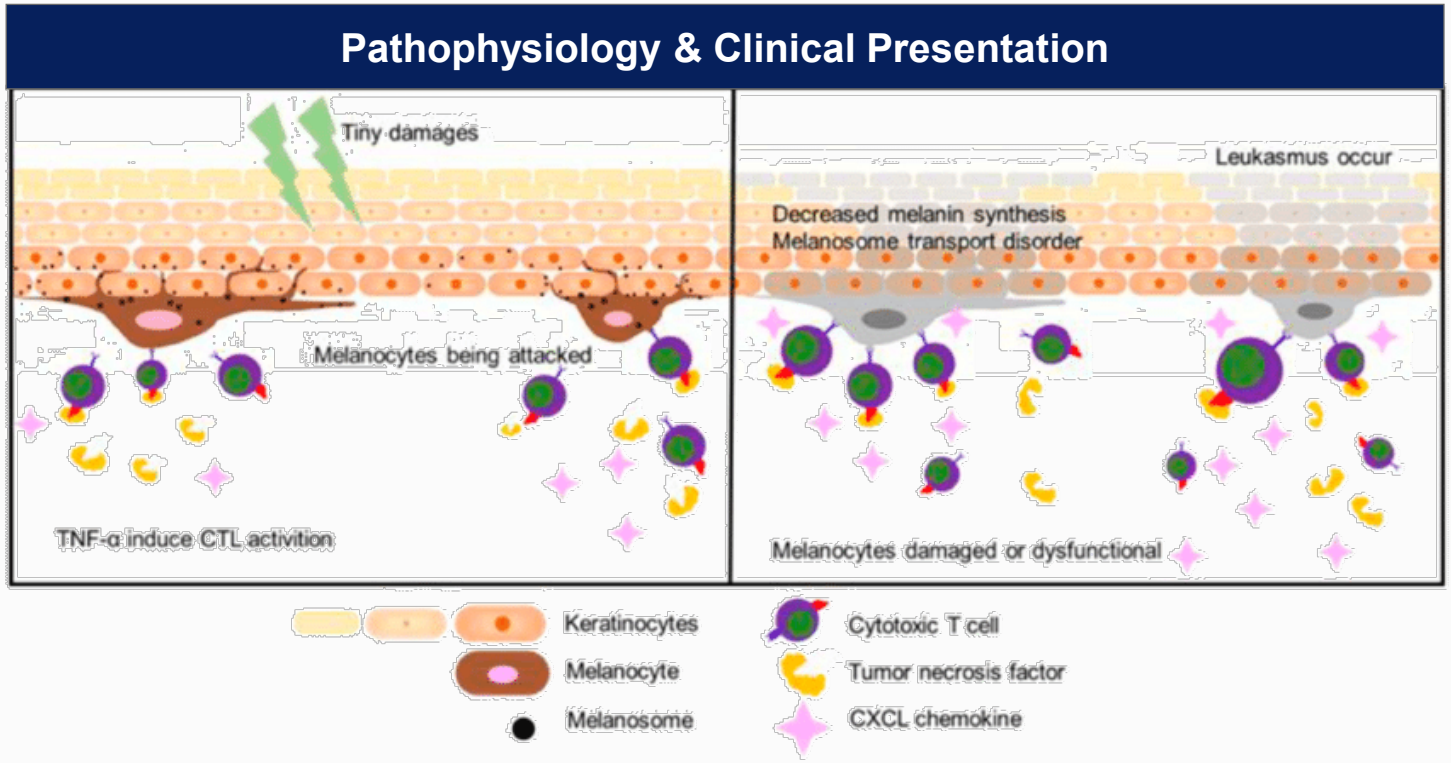
Vitiligo – Disease Overview

An acquired disorder of dermatologic pigmentation with high impact on self-esteem



- Vitiligo is a depigmenting skin disorder characterized by the **loss of melanocytes,** which causes typical non-scaly, chalky-white macules
- Pathogenesis is classified as **autoimmune in nature**; the disease is associated with a culmination of genetic and environmental factors with metabolic, oxidative stress, and cell detachment abnormalities
- Vitiligo can be classified as segmental or non-segmental; segmental presentation appears **unilaterally**, while non-segmental presents **bilaterally and occasionally mucosally** (i.e., around the mouth)
- Characteristic amelanotic lesions, while physically harmless, **tend to be psychologically devastating**

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

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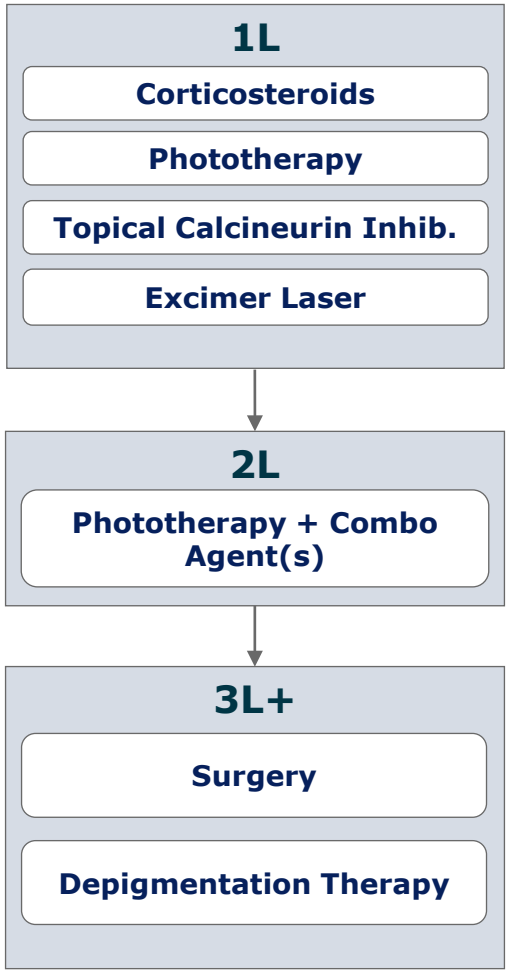
Vitiligo – Treatment Paradigm

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

Current Treatment Paradigm



Treatment modality is dependent on **disease area** (segmental vs. non-segmental) as well as **activity** (controlled vs. uncontrolled); patients typically receive **NBUVB phototherapy, excimer laser procedure,** or an **oral / topical anti-inflammatory agent in the 1L**

1L agents are often **used in combination in the 2L** to enhance disease control

Surgeries include skin tissue / cellular grafting and hair follicle transplant, often **technically challenging and costly**; depigmentation therapy is a **less common FDA-approved modality for cosmetic improvement**

Vitiligo Key Unmet Need

Current vitiligo treatment is dominated by non-specific therapeutics with only one drug recently approved with a black box warning

A **targeted, safe and more efficacious treatment option is needed** that lowers the disease recurrence rate and is effective for all skin tones / scar types

Source: UptoDate; Bergqvist. Dermatol. 2020;236:571-592; Karagaiah. Expert Opin Emerg Drugs. 2020;25(1):7-24
NBUVB: Narrow-band ultraviolet-B light

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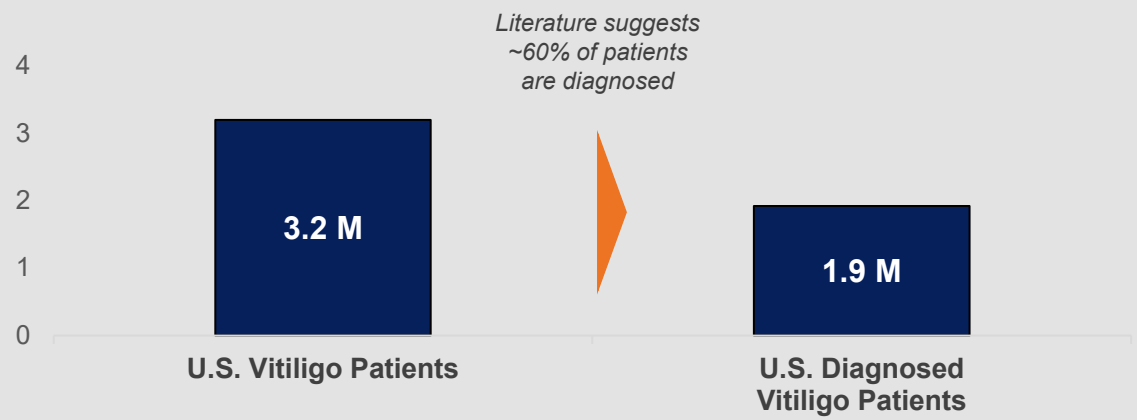
Vitiligo – Epidemiology and Pricing

Large market with high unmet need and lack of approved prescription treatment options

U.S. Addressable Patients



- **Large U.S. market U.S. Patients with Vitiligo: ~3.2 M with only 1 approved Rx drug treatment**
  - Prevalence generally consistent across regions of the world with a range of 0.5% to 2.0% of the worldwide population
- **Prevalent U.S. Patients with Diagnosed Vitiligo: ~1.9 M**
  - ~60% of prevalent vitiligo in the U.S. is clinically-diagnosed
  - Literature suggests that many patients do not currently seek treatment due to lack of approved and effective treatment options

U.S. Pricing Potential / Analogs

- A topical product as an alternative to steroids and/or calcineurin inhibitors or a JAK with black box warning would be well-received in a market with limited approved therapies;
- Anticipate payer and market access landscape to be favorable
- A relevant price comparator for a novel treatment of vitiligo may be newly FDA-approved Opzelura™ (ruxolitinib), **a topical JAK inhibitor with a black box warning, targeting AD and vitiligo (July 2022)**
- Opzelura™ is priced at ~$2 K per 60g tube or $20 K annually assuming guidance ~10 tubes on average per year for vitiligo

Current Annual Opzelura Price Expectation:

~$20 K

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; Incyte Corporate Pres.; Redbook; Rxlist.com MOA: Mechanism of action; sNDA: Supplemental new drug application.[1] Data also suggest a small percentage of pediatrics (i.e., 0.24%) affected by vitiligo; Vitiligo prevalence is fairly-consistent across different regions according to Kruger (2012)

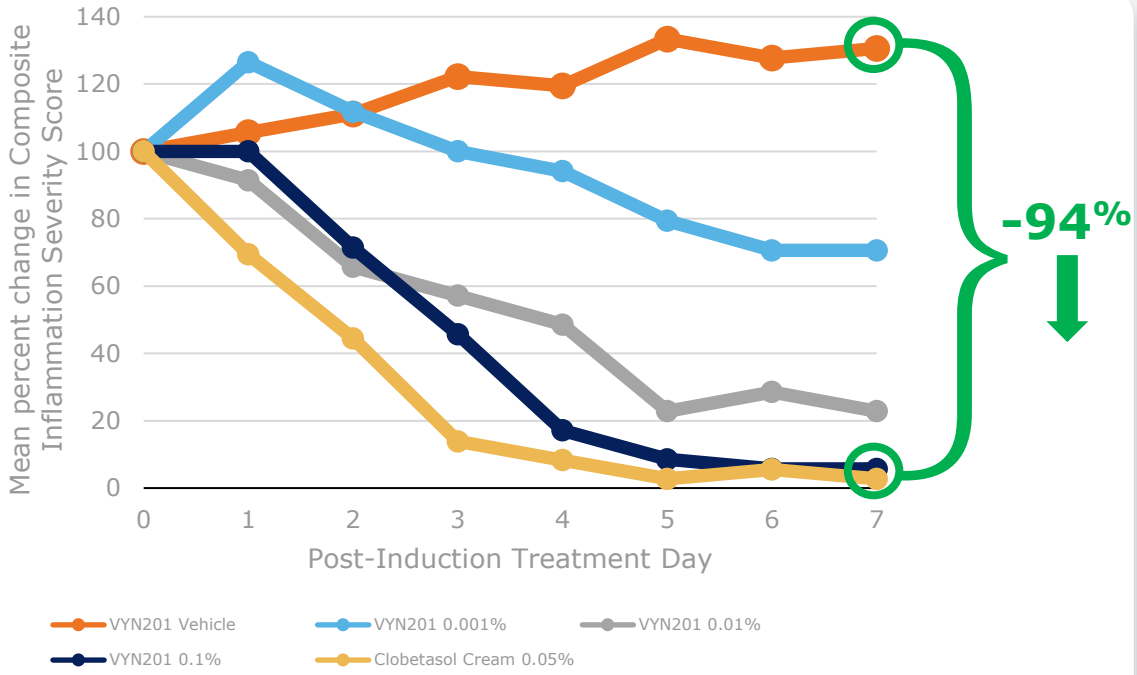
VYNE™ THERAPEUTICS

VYN201: Th17 Inflammation Model

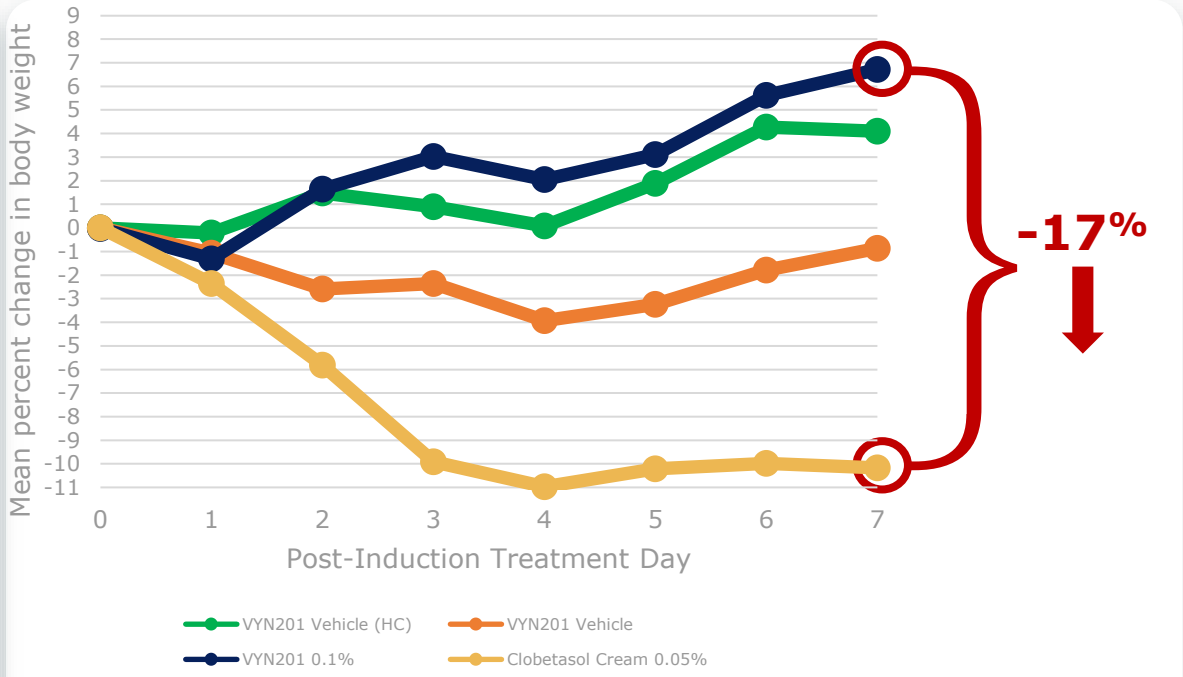
VYNE™ THERAPEUTICS

VYN201: Comparable Efficacy to Superpotent Steroid Clobetasol
in a TH17-Mediated Murine Inflammation Model; Potential for Greater Tolerability

Dorsal depilated BALB-C mice were dosed topically for 14 days with 100mg topical IMI cream (Day 1-7: induction phase, Day 8-14: treatment phase). N=4 animals were assigned to each treatment group with each group receiving 100mg of allocated treatment on Day 8-14 once daily



- Dose dependent response was observed over the VYN201 concentration range 0.001% to 0.1%
- There was a 94% reduction in composite score for VYN201 0.1% relative to vehicle control group at Day 7
- VYN201 0.1% had comparable efficacy to clobetasol propionate 0.05% cream



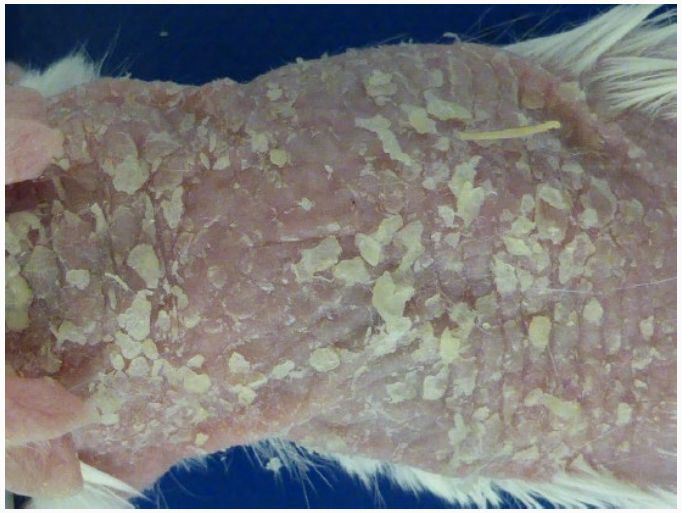
- Animals treated with VYN201 0.1% continued to gain body weight in a similar manner to healthy control group treated with vehicle
- Clobetasol cream 0.05% group had a 17% reduction in body weight compared to the VYN201 0.1% group at treatment day 7

IMI – Imiquimod.

*Composite Inflammation Severity Score is a composite mean score of erythema and peeling severity scored on a 4-point ordinal scale per domain (0=none, 1=mild, 2=moderate and 3=severe for a maximum score of 6), data expressed as a mean percentage change from initiation of treatment phase.

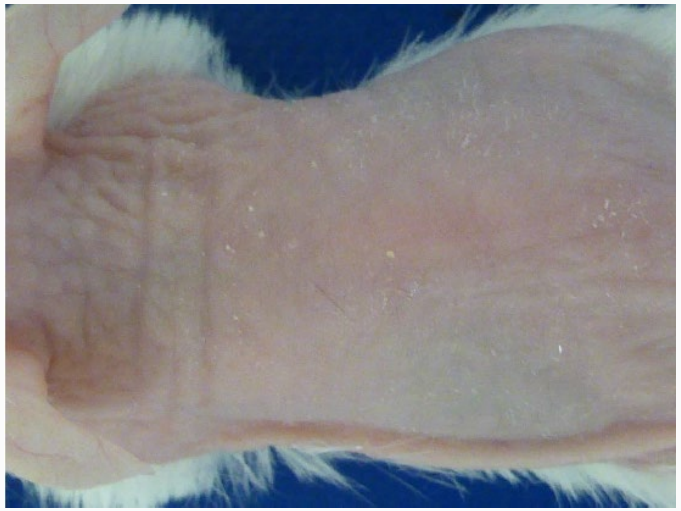
VYNE™ THERAPEUTICS

VYN201:
Normal Skin Physiology in TH17-Mediated Murine Inflammation Model Suggests VYN201 Well Tolerated (Day 7)



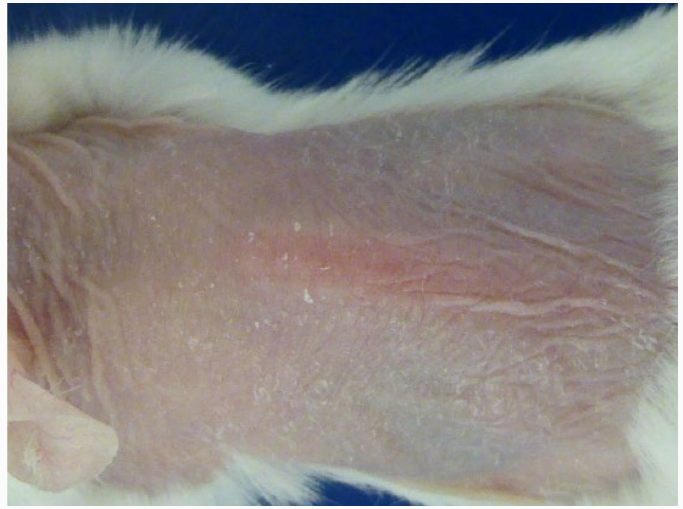
VYN201 Vehicle

- No appreciable improvement in clinical signs



VYN201 0.1%

- Substantial resolution of clinical signs
- Skin presents with normal physiology with no evidence of striae rubrae or atrophy
- No evidence suggestive of intolerance

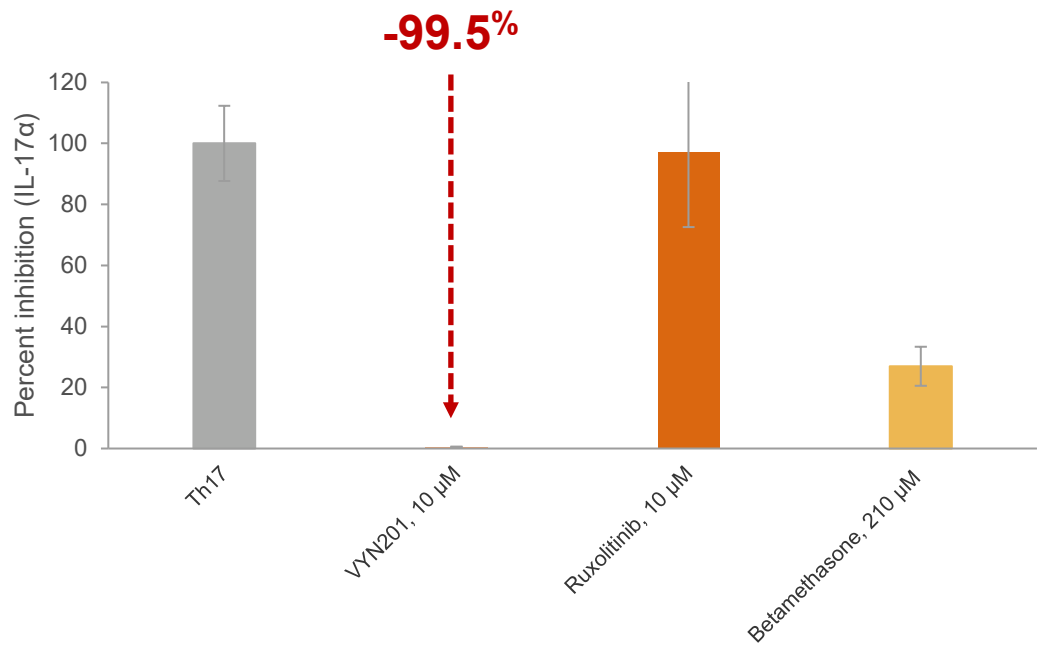


Clobetasol Cream 0.05%

- Substantial resolution of clinical signs
- Significant evidence of dermal atrophy (clear presence of both rhytides/fine wrinkles and deep wrinkles)
- Marked dermal translucency and elastolysis

VYNE™ THERAPEUTICS

VYN201 Significantly Reduced Expression of Several Key Pro-Inflammatory Proteins Relevant to Th17-mediated Autoimmune Diseases in Human Tissue[1]



Interleukin 17-alpha

T-cells are polarized to Th1 and Th17 cells, the latter of which drives the production of IL17a which further upregulates the migratory action of pro-inflammatory cells and further inflammatory cell activation.

>95% Inhibition seen with assays for IL-36γ & LP-10

Interleukin 36-gamma

IL36γ is implicated in upregulating IL-17A signaling-related genes and so able to amplify keratinocyte inflammatory responses by promoting not only their own expression but also that of other cytokines related to Th17 signaling

CXC motif chemokine ligand 10 (LP-10)

An inflammatory cell chemoattractant secreted in response to interferon gamma. LP-10 is significantly overexpressed in many autoimmune diseases (>25-fold) vs. healthy skin[1]

1. Data on file. Results presented from qPCR analysis of processed and Th17-stimulated ex vivo human skin tissue based on a method derived from Garrett S.M., Zhao Q., and Feghali-Bostwick C. (2019) Induction of a Th17 phenotype in human skin – a mimic of dermal inflammatory diseases, *Methods and Protocols*, 2, 45

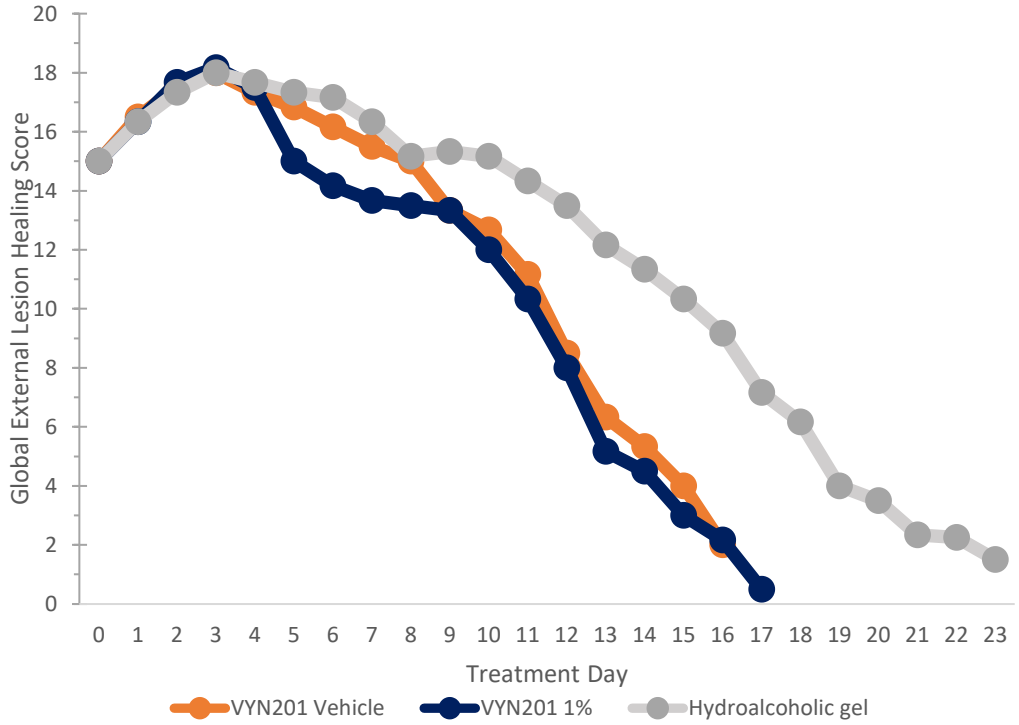
VYNE™ THERAPEUTICS

VYN201: Fibrotic Tissue & IPF Models

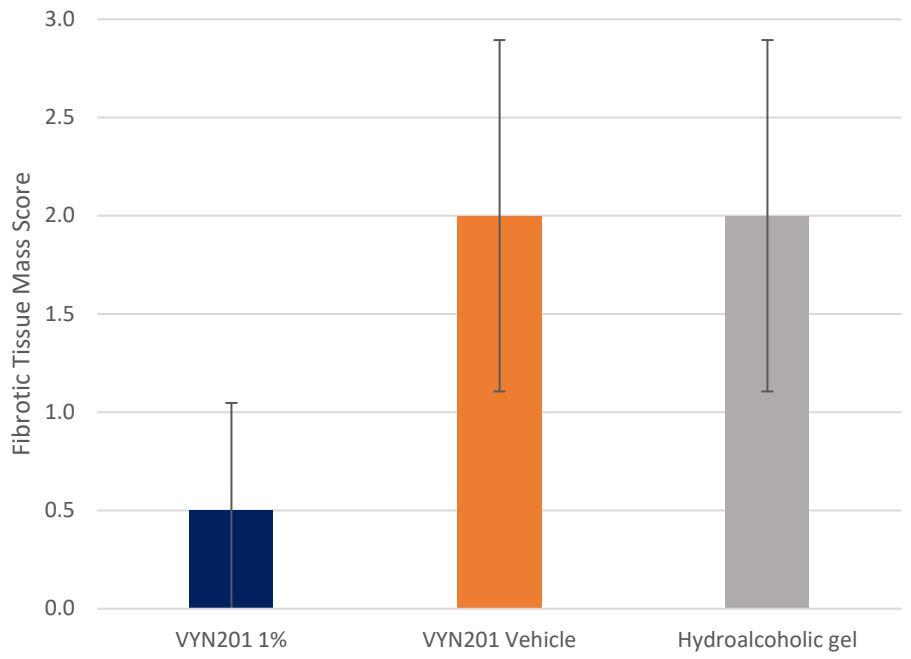
VYNE™ THERAPEUTICS

VYN201: Demonstrated Anti-Fibrotic Activity
without Delay in Healing Time in Murine Skin Healing Model

Female hairless mice (n=4/group) had two identical 10mm incisions made either side of the flank. Animals were topically dosed 1X daily with 100mg VYN201 vehicle, VYN201 1% or a Hydroalcoholic gel* until each wound had completely healed



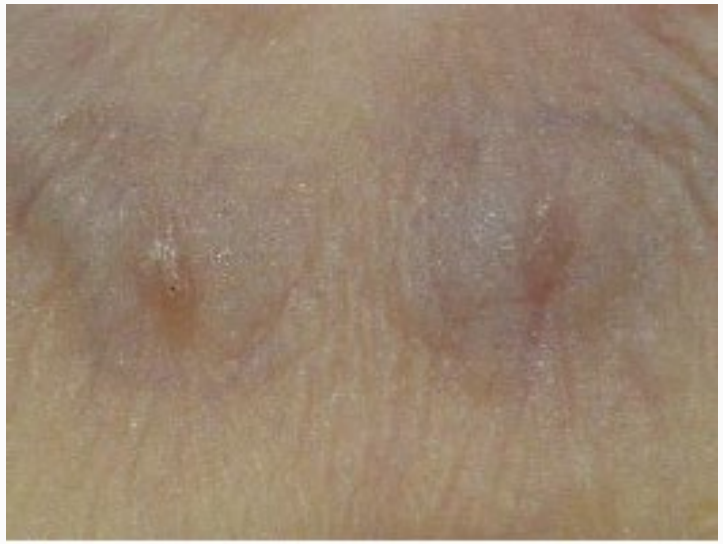
- Statistically significant difference ($p<0.05$) in composite global external healing score for VYN201 1% compared to Hydroalcoholic gel from Day 8
- Complete healing occurred for VYN201 1% and VYN201 vehicle approximately 5 days earlier compared to Hydroalcoholic gel (Mean day to heal:15.5 vs. 21 days)



- Animals treated with VYN201 1% had statistically significant less tissue mass/fibrosis compared to VYN201 vehicle or Hydroalcoholic gel, indicative of the known anti-fibrotic mechanism for BET inhibition ($P<0.05$ for VYN201 1% compared to VYN201 vehicle and Hydroalcoholic gel)

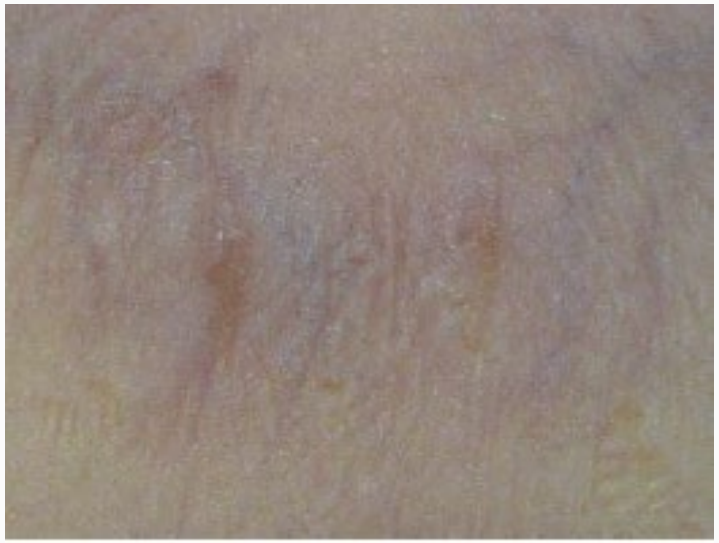
*A negative control known to delay wound healing
Global External Lesion Score is a composite severity score of lesion length, width, swelling and visibility
Fibrotic tissue mass is scored on a 4-point severity scale: 0=No tissue mass; 1=small tissue mass; 2=moderate tissue mass; 3=large tissue mass

VYN201: Little Evidence of Residual Swelling
and Macular Wound Appearance in Murine Skin Healing Model



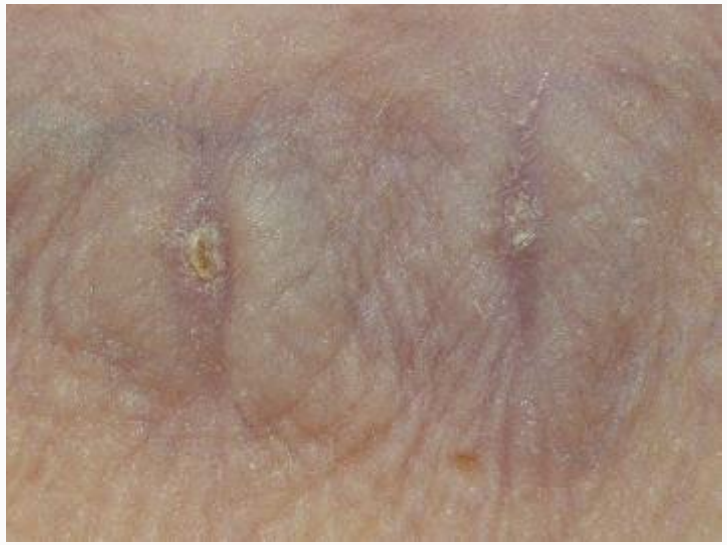
VYN201 Vehicle

- Still evidence of minor swelling around incision sites



VYN201 1%

- Little evidence of residual swelling
- Wound appears more macular in nature compared to VYN201 vehicle or the Hydroalcoholic gel
- Incision sites appear less distinct and leave a more aesthetic outcome compared to other treatments

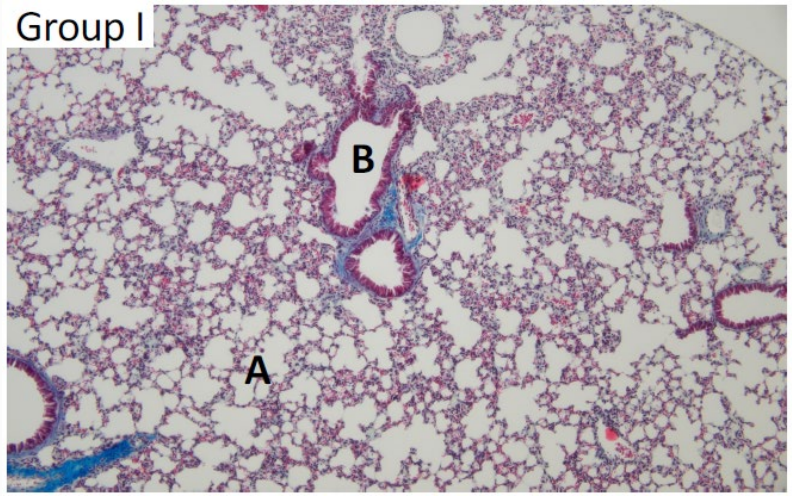


Hydroalcoholic gel

- Moderate swelling clearly evident at end of treatment
- Although healed, residual scabbing still remains
- Incision sites clearly visible

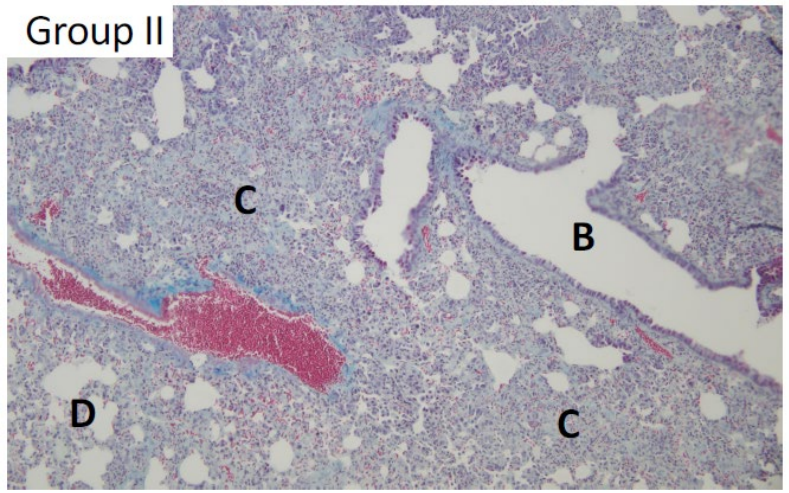
VYN201: Bleomycin-induced mouse model of IPF - Histology

Histology images indicate positive impact of VYN201 0.06mg/ml on fibrosis in lungs. Additional preclinical exploration planned



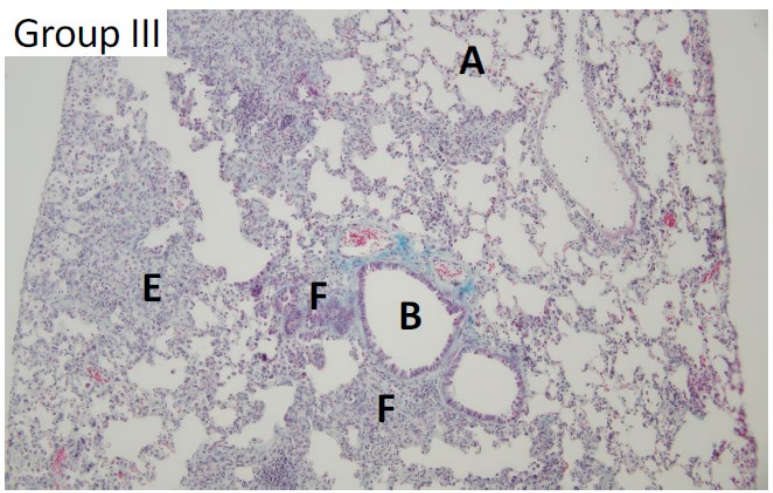
Healthy sham control

A: Normal lung parenchyma with open airways and airspaces.
B: Conducting airway



Bleomycin control

B: Conducting airway
C: Fibrotic lesions with abundant cellularity
D: Sporadic airways



Bleomycin + 0.06mg/ml VYN201

A: Normal lung parenchyma with open airways and airspaces.
B: Conducting airway
E: Less severe localized fibrosis: parenchyma
F: Less severe localized fibrosis: airway

*Lung fibrosis is induced in C57bl/6 mice using bleomycin at a dose of 4U/kg once daily by intranasal administration (N=10/treatment group). VYN201 treatment groups received nebulized, intra-nasal doses at 0, 0.06, 0.6 and 3mg/ml and bleomycin concomitantly for 21 days. A sham group received vehicle only.

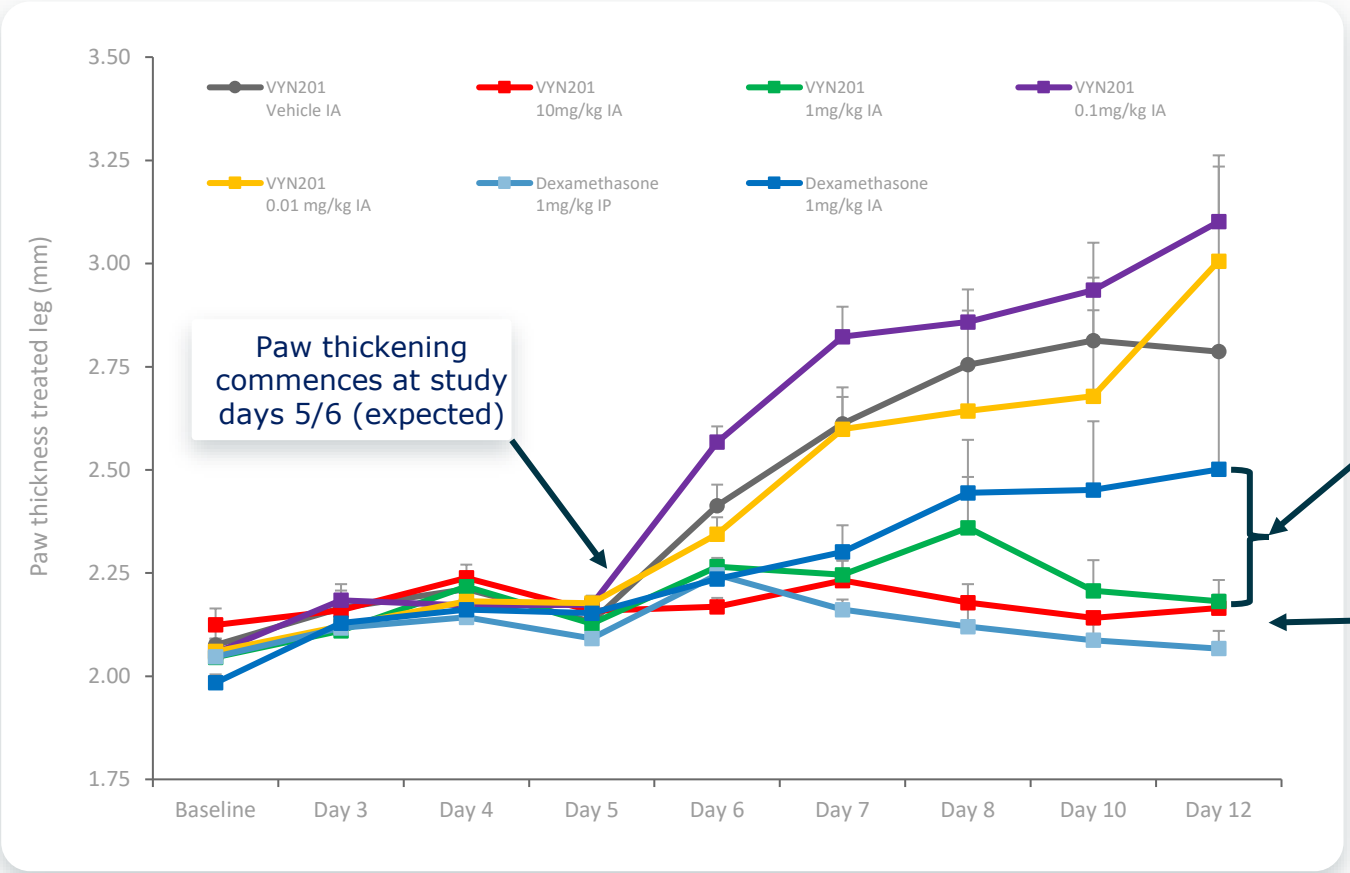
VYNE™ THERAPEUTICS

VYN201: Arthritis

VYN201: CAIA Mouse Model of Arthritis – Paw Thickness

Marked inhibition of paw thickening/swelling

Inflammatory arthritis was induced in BALB/C mice using a mixture of four arthritogenic MAbs by IV injection at Day 0 and was further challenged with an LPS IV injection at Day 4 (N=7/treatment group). VYN201 treatment groups received 50µl intra-articular (IA) doses of VYN201 at 0, 0.01, 0.1, 1 or 10mg/kg on Days 0, 3, 6 and 9. Dexamethasone control animals received 50µl of 10mg/kg IA on Days 0, 3, 6 and 9 or 1mg/kg intraperitoneal (IP) on each treatment day (Day 0-11). Treatment response was evaluated based on an assessment of paw thickening/swelling.



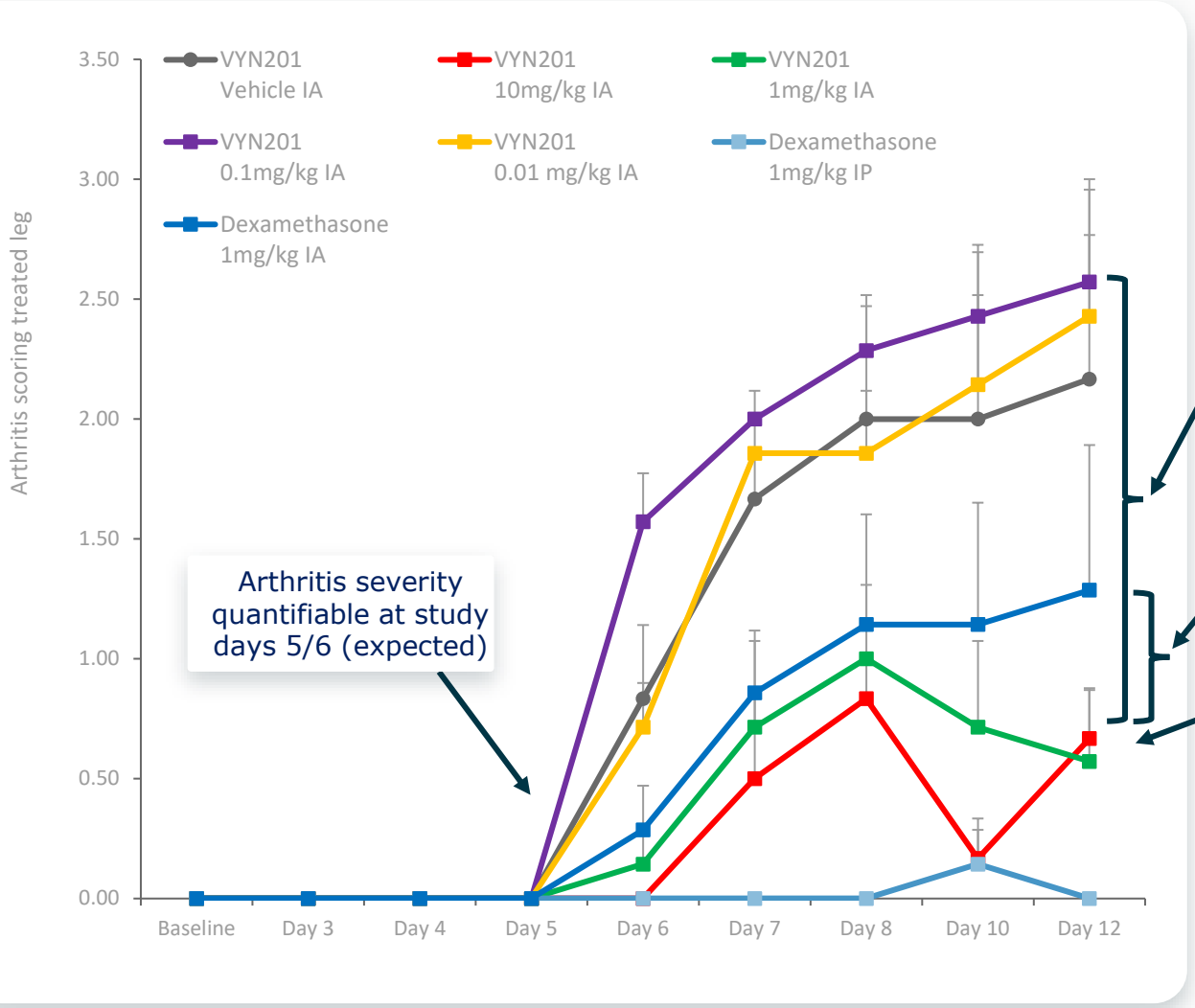
Both VYN201 1 & 10mg/kg superior to dexamethasone IA 10mg/kg

Marked inhibition of paw thickening for the VYN201 1 & 10mg/kg dose levels and in line with 1mg/kg dexamethasone systemic dose

CAIA = Collagen Antibody Induced Arthritis; IA = Intra-articular; IP = Intraperitoneal

VYN201: CAIA Mouse Model of Arthritis – Arthritis Score

Demonstrated dose dependent reduction in disease severity



Clear dose-response demonstrated between VYN201-treated groups

Both VYN201 1 & 10mg/kg superior to dexamethasone IA 10mg/kg

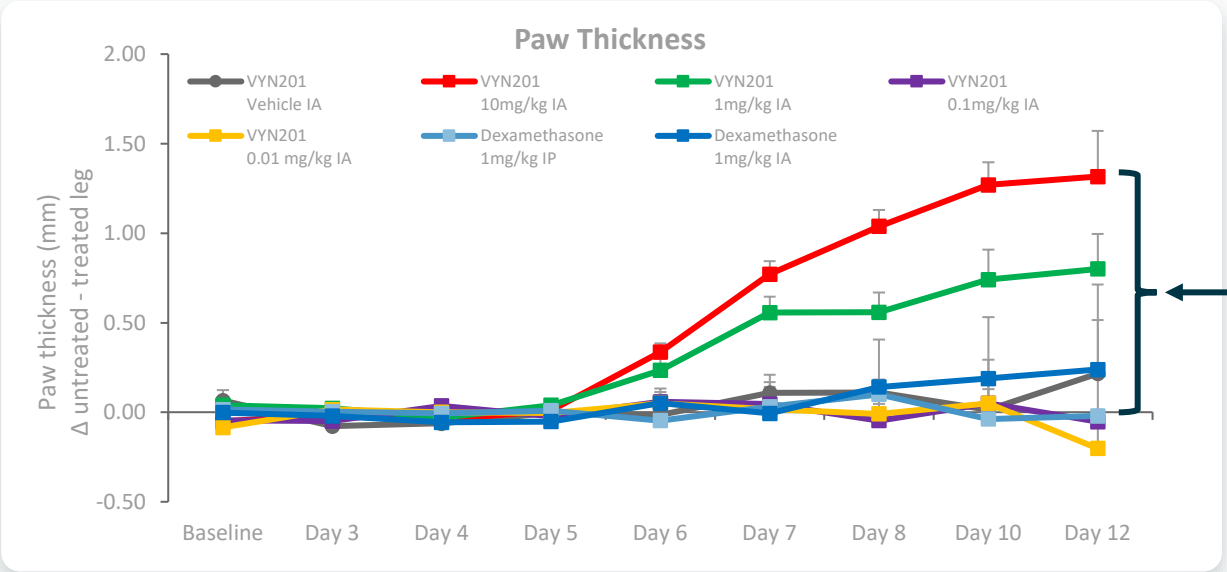
Marked inhibition of arthritis signs and symptoms for VYN201 at 1 & 10mg/kg dose levels with severity scores approaching "normal" (mean severity score <1)

*Scoring based on a five-point composite severity scale of redness, swelling of the ankles and wrists, and paw thickness. Scoring ranges from 0 (normal) to 4 (extensive signs and symptoms of arthritis);
CAIA = Collagen Antibody Induced Arthritis; IA = Intra-articular; IP = Intraperitoneal

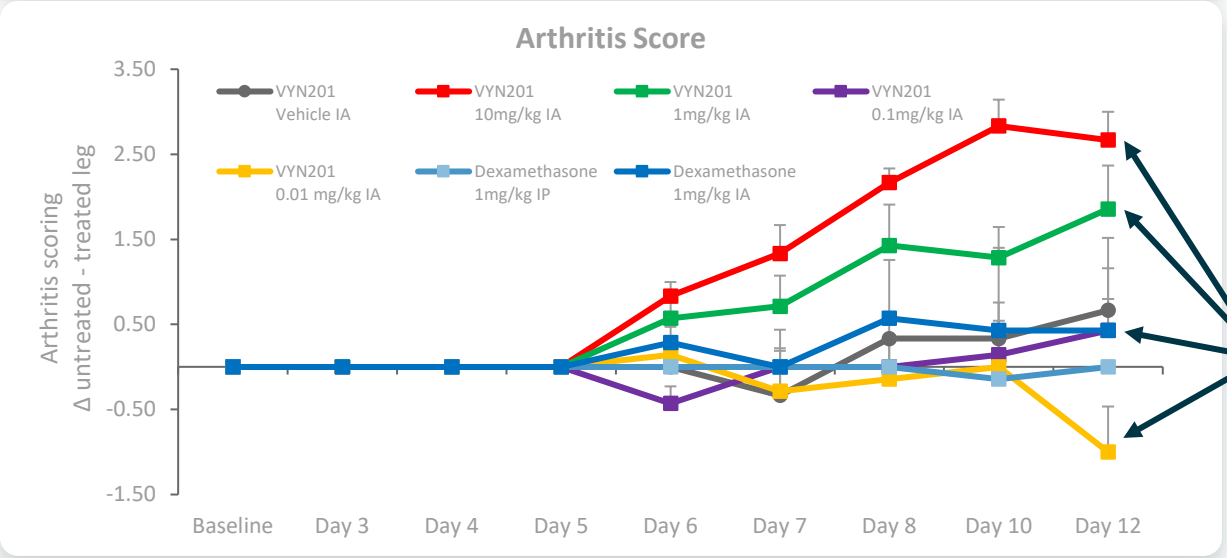
VYNE™ THERAPEUTICS

VYN201: CAIA Mouse Model of Arthritis – Systemic Impact

Demonstrated localized dose-dependent effect



VYN201 1 & 10mg/kg results demonstrated the highest localized effect in the treated limb when compared to the untreated limbs (largest delta between treated and untreated limbs)



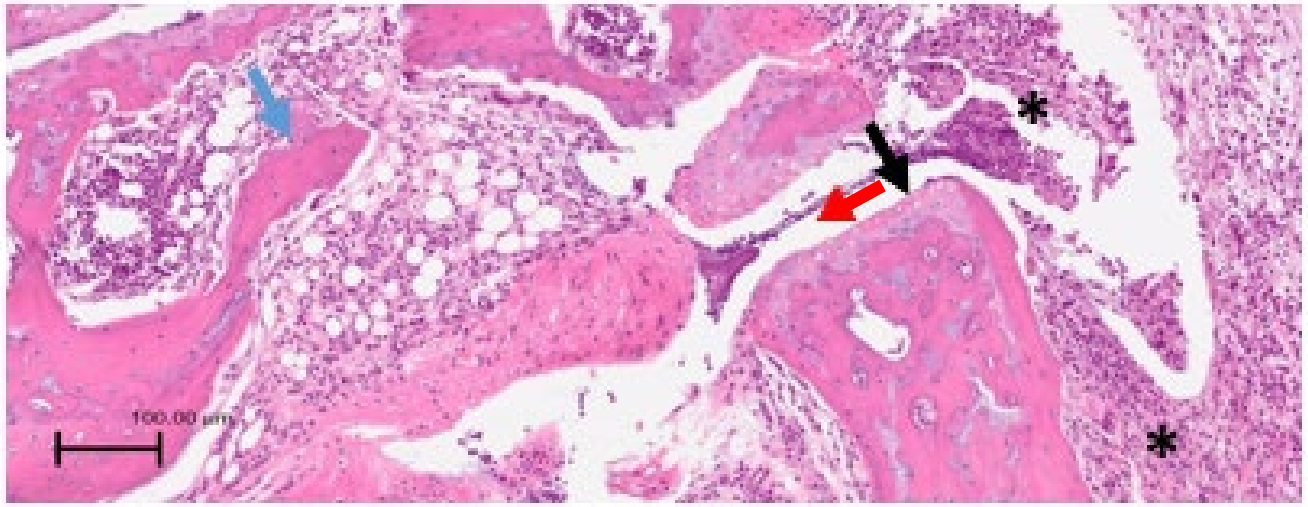
Treatment effect for VYN201 treated animals was dose-dependent over the dose range 0.01 to 10mg/kg

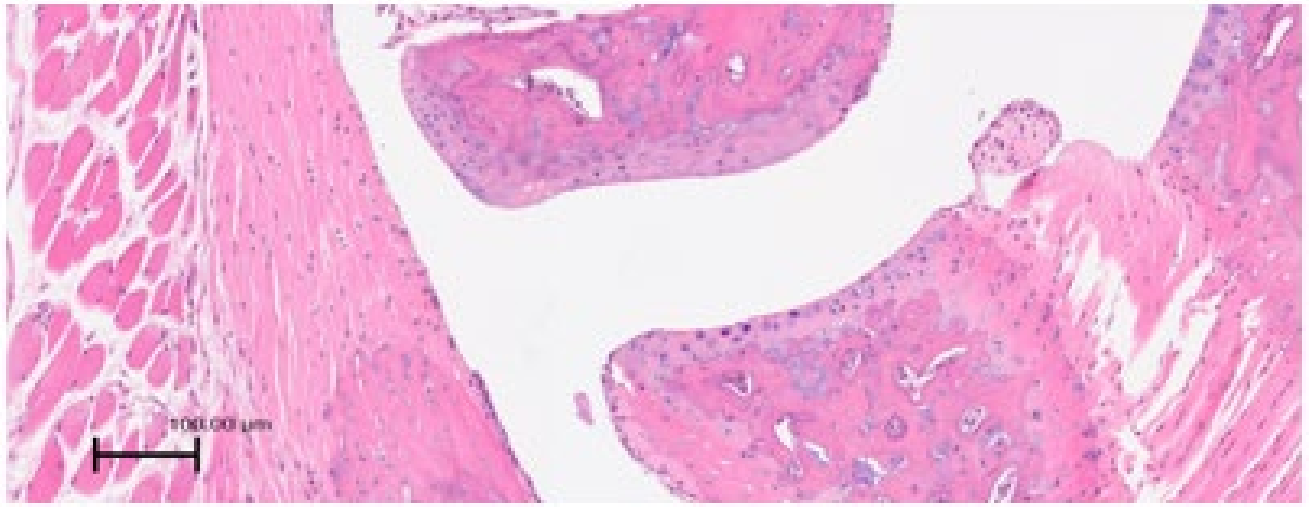
*Scoring based on a five-point composite severity scale of redness, swelling of the ankles and wrists, and paw thickness. Scoring ranges from 0 (normal) to 4 (extensive signs and symptoms of arthritis); CAIA = Collagen Antibody Induced Arthritis; IA = Intra-articular; IP = Intraperitoneal

VYN201: CAIA Mouse Model of Arthritis – Histopathology

Joint histopathology confirmed arthritis clinical scoring & local effect

Inflammation marked with asterisk; damage to bone marked with a blue arrow; inflammatory cells and cellular debris in the joint space marked with red arrow; damage to cartilage marked with black arrow; scale bar-100µm





VYN201 10mg/kg treatment group

Untreated right paw

- Arthritis score 4 "severe"
- Severe inflammation with destruction of both cartilage and bone

Treated left paw

- Arthritis score 0 "within normal limits"
- No evidence of inflammatory cell infiltrate in the joint spaces

Appendix:
FMX114
Tofacitinib and Fingolimod Topical Gel for AD

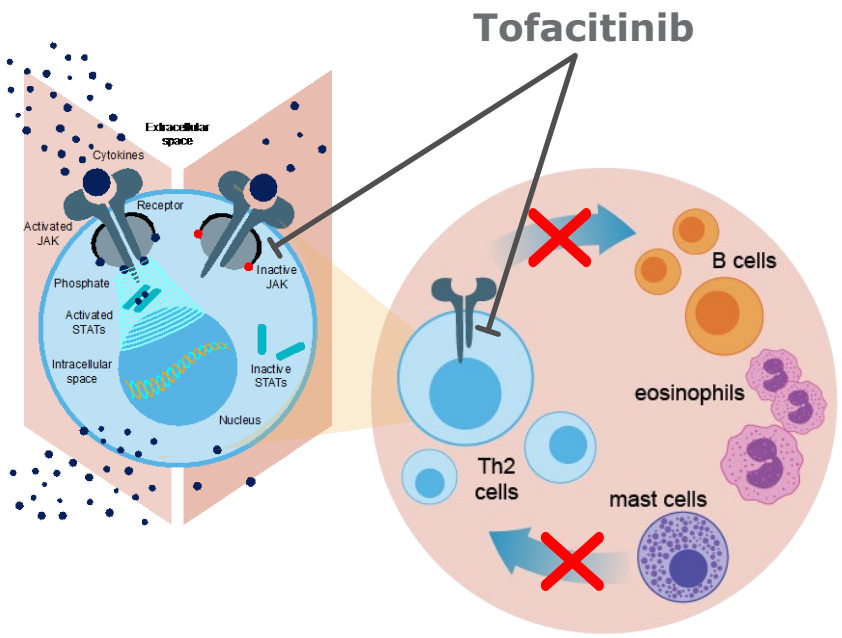
VYNE™ THERAPEUTICS

ROOTED IN INNOVATION

FMX114: Two Validated Modes of Action

Designed to address both the source & cause of inflammation in AD

Tofacitinib (Janus kinase Inhibitor) Reduces inflammation intracellularly by inhibiting cytokine release from inflammatory cells[1]



Fingolimod (Sphingosine 1-phosphate receptor modulator) Reduces inflammation by inhibiting migration of inflammatory cells[2]. May directly support upregulation of filaggrin and skin barrier recovery[3,4]

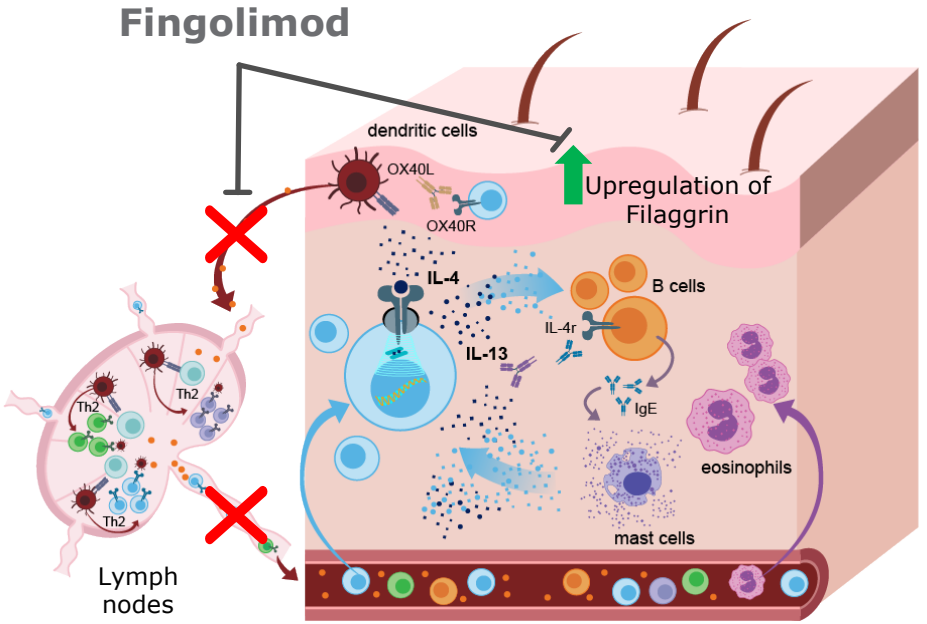


Image Sources: Leung DY, Guttman-Yassky E. *J Allergy Clin Immunol*. 2014;134(4):769-779 and Hodge JA, Kawabata TT, Krishnaswami S et al. *Clin & Exper Rheum*. 2016; 34(2): 318-328

1. Schwartz DM, Kanno Y, Villarino A, Ward M, Gadina M and O'Shea JJ, Nat Rev Drug Discov. 2017 Dec 28; 17(1):78
2. Czeloth N, Bernhardt G, Hofman F, Genth H and Forster R, J Immunol, 2005 Sep; 175(5): 2960-2967
3. Allende ML, Sipe LM, Tuymetova G, Wilson-Henjum KL, Chen W and Proia RL, J Biol Chem. 2013 Jun 21; 288(25): 18381–18391
4. Tsuji T, Okuno S, Kuroda A, Hamazaki J, Chikami T, Sakurai S, Yoshida Y, Banno R, Fujita T and Kohno T, Allerg. Int., 2016; 65: 172-179

VYNE™ THERAPEUTICS

FMX114:
Targeting A Multi-factorial Solution for a Multi-factorial Disease

Comparison to select topical products approved or in development for the treatment of AD:

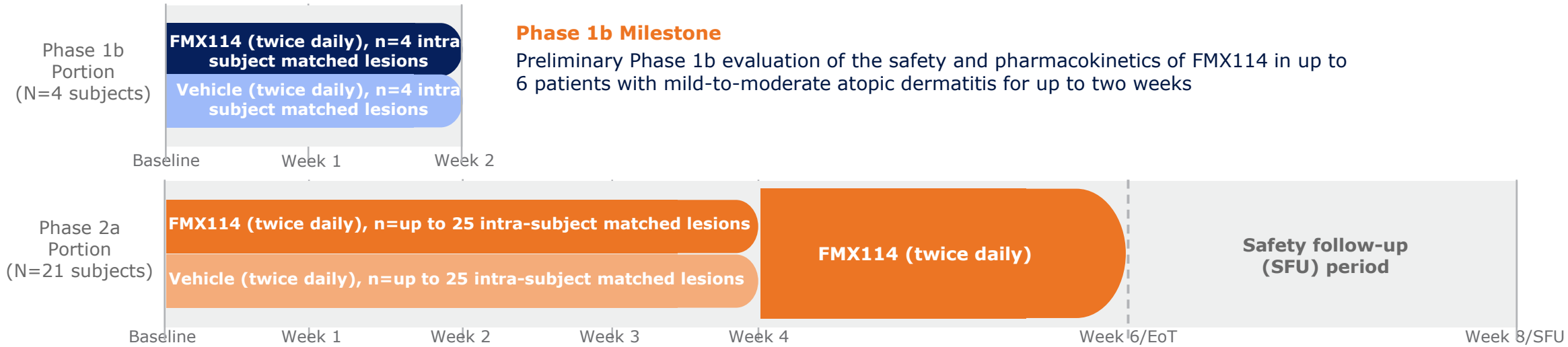
Characteristic	FMX114 Target Profile	JAK Inhibitors	PDE4 Inhibitors	Aryl hydrocarbon receptor Agonists	Gluco-Corticosteroids	Calcineurin Inhibitors
Moderate-to-severe patient indication	✓	✓	✗	✓	✗	✗
Multiple validated modes of action	✓	✗	✗	✗	✗	✗
Rapid onset of treatment effect	✓	✓	✓	✗	✓	✓
Potential for direct skin barrier repair	✓	✗	✗	✗	✗	✗
Skin collagen depletion/scarring risk	Low	Low	Low	Low	High	Low
Dermal "rebound" potential	Low	Low	Low	Low	High	Low
Local tolerance issues (e.g. burning/stinging)	Low	Low	Low Moderate	Low	Moderate	Low

Source: Data on file

VYNE™ THERAPEUTICS

FMX114 Phase 1b/2a Proof of Concept Study Design

Randomized, double-blinded, vehicle-controlled Phase 1b/2a trial with separate open-label active treatment phase evaluating the safety, pharmacokinetics & efficacy of FMX114 gel vs. vehicle gel in the treatment of mild-to-moderate atopic dermatitis



Phase 1b Milestone

Preliminary Phase 1b evaluation of the safety and pharmacokinetics of FMX114 in up to 6 patients with mild-to-moderate atopic dermatitis for up to two weeks

Key Inclusion criteria

- Healthy males/nonpregnant females, aged ≥ 18 years at screening visit
- Mild (2)-to-moderate (3) atopic dermatitis on ≤ 35% BSA (excluding face, scalp, and groin)
- Presence of 2 comparable target lesions 10 to 200 cm^2 of surface area and located on the trunk, upper extremities, or lower extremities
- A target lesion Atopic Dermatitis Severity Score (ADSI) of ≥ 6 and ≤ 12, with a between-lesion difference in ADSI of ≤ 1

Safety and efficacy endpoints/assessments

- Treatment emergent adverse events
- Local skin tolerability assessments
- Clinical laboratory assessments (hematology, chemistry, urinalysis and FSH), Physical exam/vitals
- 5 different Clinical assessment scores

FMX114 Phase 1b Safety and Pharmacokinetics

Highlights

- Systemic bioavailability of JAK inhibitor (tofacitinib) and S1P receptor modulator (fingolimod) in topical formulation substantially lower compared to oral equivalents
- Mean Cmax of tofacitinib 50-fold and 1500-fold lower at Day 1 and 14 of study compared to the lowest commercially available oral alternative

Safety

- FMX114 and vehicle generally well tolerated with no treatment-emergent SAEs.
- No clinically-significant adverse events of special interest related to either tofacitinib or fingolimod.
- Local application site tolerance to both treatments remained high throughout treatment.

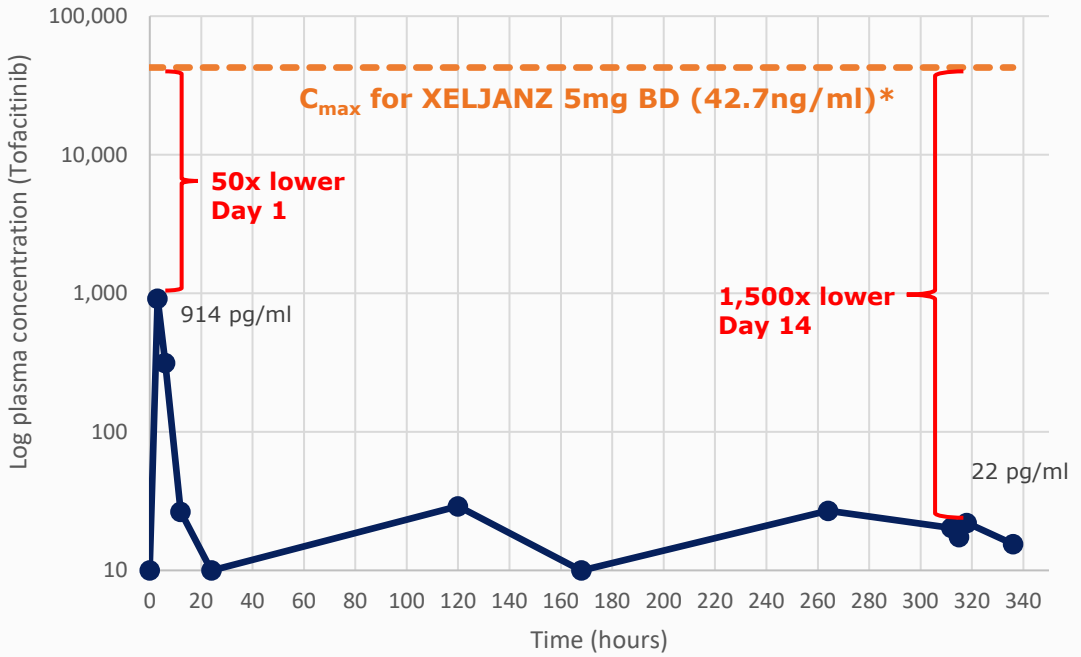
Tofacitinib Pharmacokinetics

- Mean plasma C_{max} on Day 1 and Day 14 are approximately 50-fold and 1500-fold lower, respectively, when compared to the lowest commercially available adult oral dose of tofacitinib (XELJANZ 5mg BD, C_{max}: 42.7ng/ml).
- No systemic drug accumulation of tofacitinib observed over the dosing period.

Fingolimod & Fingolimod 1-Phosphate Pharmacokinetics

- Not determinable. All blood concentrations of fingolimod and fingolimod 1-phosphate were below assay LLOQ (0.08ng/ml).

Log mean tofacitinib plasma concentration by time



* XELJANZ Prescribing Information December 2021, accessed January 2022.
SAE: Serious Adverse Event; C_{max}: maximum plasma concentration; AUC_{24}: Area Under the Curve (0-24hr); LLOQ: Lower Limit Of Quantification.

FMX114 Phase 2a Efficacy Data

Highlights

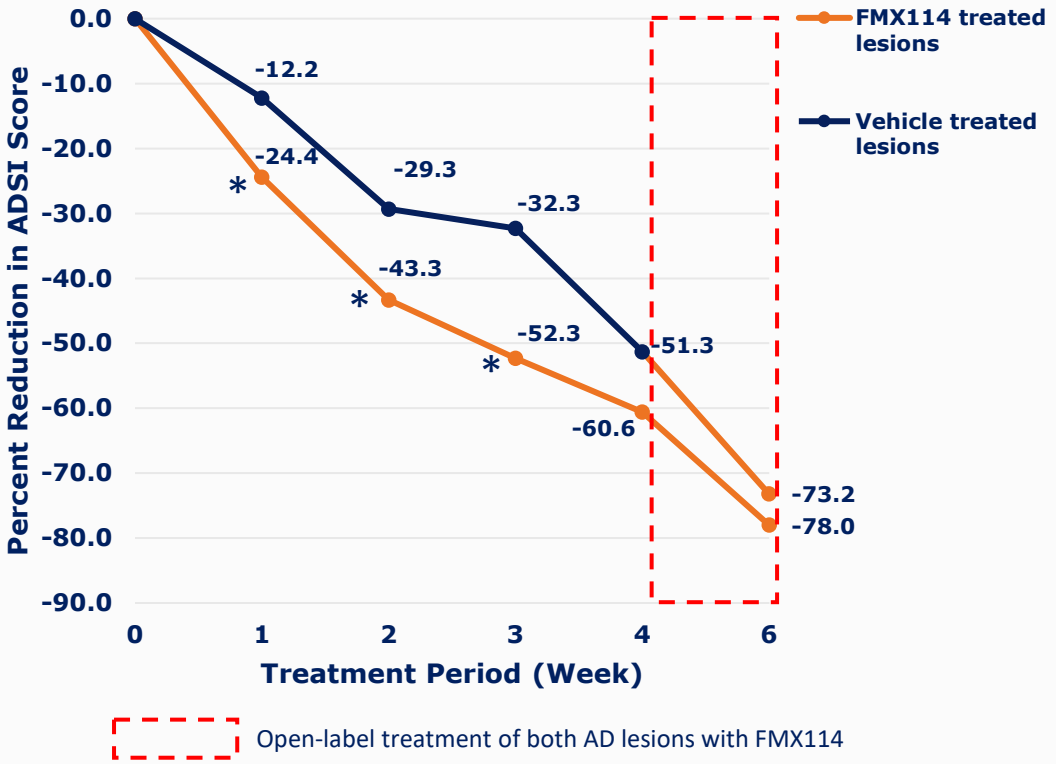
- Efficacy data for the Phase 2a trial was measured based on the absolute and percent change relative to baseline in the ADSI scoring assessment at week 4:
  - FMX114 was statistically superior to vehicle up to and including week 3; numerically superior at week 4 (primary endpoint missed)
- FMX114 efficacy results continue to improve beyond 4 weeks of treatment

Absolute and percent change relative to baseline in ADSI score:

- Mean ADSI scores for FMX114 and vehicle treated lesions were 6.6 and 6.9, respectively, at baseline.
- Mean reduction in ADSI from baseline was -4.1 (-60.6% mean reduction) for FMX114 treated lesions compared to -3.5 (-51.3% mean reduction) for vehicle treated lesions at Week 4 (p=0.228, OC, ITT).
- FMX114 was statistically superior to vehicle in mean percent reduction in ADSI at all post-baseline visits with exception to Week 4 during the double-blind phase.
- FMX114 efficacy results continue to improve during a two-week open-label extension (-78% mean reduction in ADSI compared to baseline)

Pruritus (itch) NRS:

- Subjects reported a -66.7% mean reduction in worst pruritus NRS from baseline for lesions treated with FMX114 compared to a -59.4% mean reduction for vehicle treated lesions at Week 4.
- Mean reduction in worst pruritus NRS from baseline at Week 6 was -85.1% for FMX114 treated lesions during double-blind phase and 85.4% for vehicle treated lesions during double-blind phase.



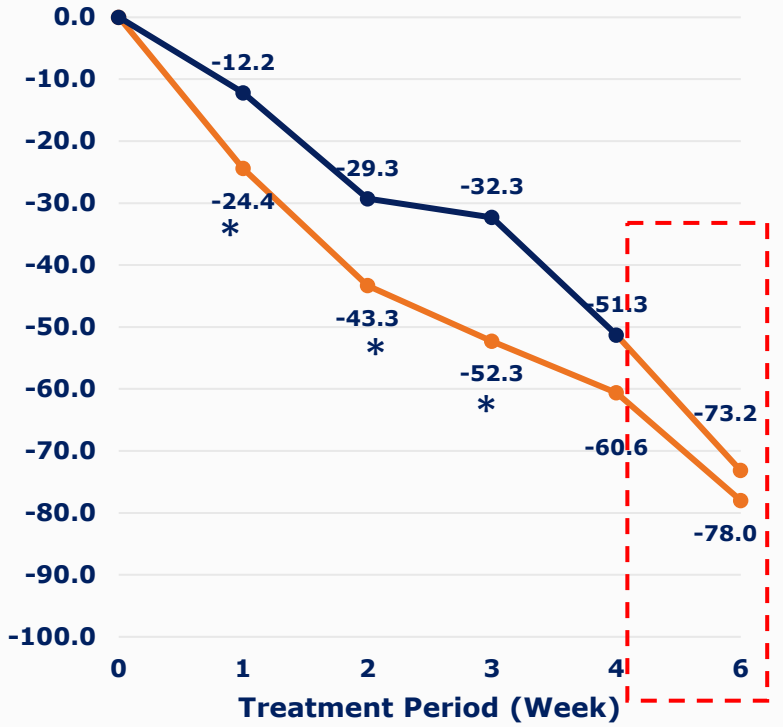
ADSI = Atopic Dermatitis Severity Score; NRS = Numeric Rating Scale

*p<0.05 – FMX114 treated lesions vs. vehicle treated lesions

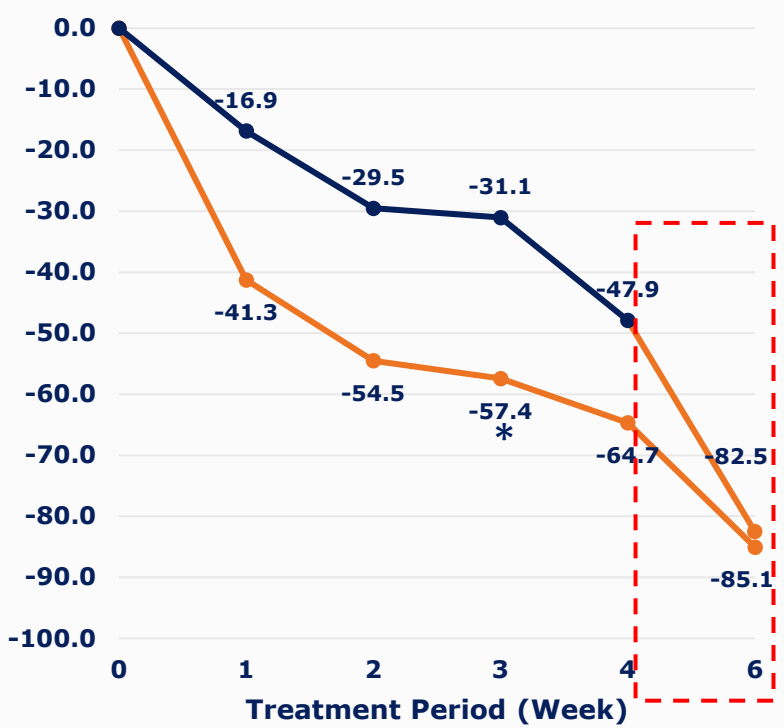
FMX114 Phase 2a Subanalyses

Percent Reduction in ADSI Score by Baseline Score

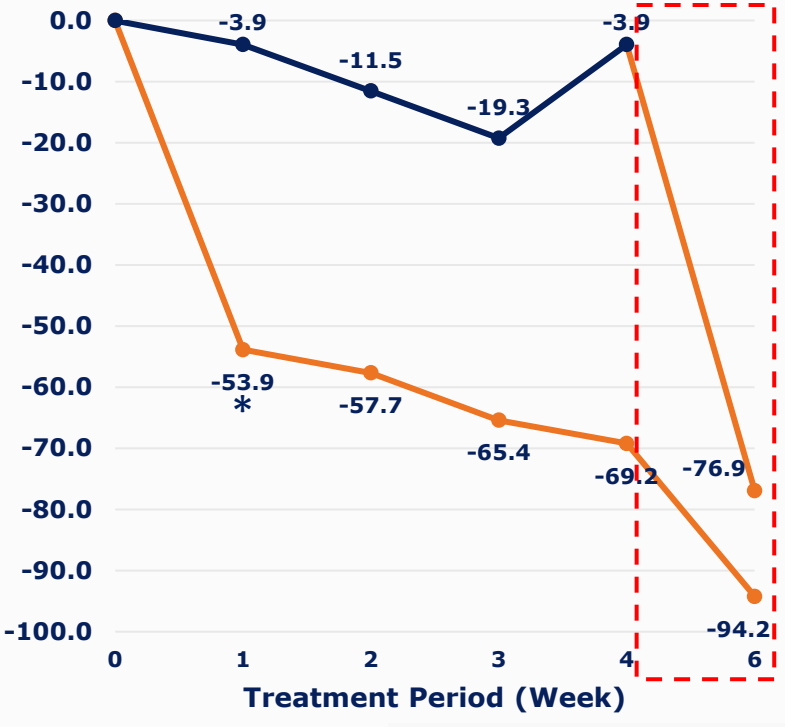
Baseline ADSI score of 6 through 9[1]
(Mean ADSI = 6.6 active; 6.9 vehicle)
(n = 21 pts.; 42 lesions)



Baseline ADSI score of 7 through 9[1]
(Mean ADSI = 7.6 active; 7.9 vehicle)
(n = 9 pts.; 18 lesions)



Baseline ADSI score of 8 through 9[1]
(Mean ADSI = 8.7 active; 8.7 vehicle)
(n = 3 pts.; 6 lesions)



- Treatment effect separation (FMX114 vs Vehicle) increases for higher baseline severities
- There is a continual development of efficacy beyond Week 4 i.e. no plateau

Open-label treatment of both AD lesions with FMX114

FMX114 treated lesions

Vehicle treated lesions

*p<0.05 – FMX114 treated lesions vs. vehicle treated lesions ADSI = Atopic Dermatitis Severity Score 1. Inclusive

FMX114 Phase 1b/2a Results Summary

- ✓ **FMX114 drug effect and <u>proof-of-concept established</u>**
  - On target PK and safety profile met
  - Statistically significant efficacy results at weeks 1, 2 and 3; Primary efficacy endpoint at week 4 not met but numerically superior
  - Continued effect demonstrated through week 6 (OLE)
  - Subanalyses show higher ADSI scores at baseline correlated with improved overall treatment effect separation of FMX114 vs. vehicle
- ✓ **Analyses suggests Phase 2a results confounded by over-enrollment of subjects with mild disease severity:**
  1. Mean ADSI scores at baseline of 6.6-6.9 suggests over-enrollment of subjects with mild disease severity, potentially resulting in elevated vehicle effect in the full study population **(inclusion criteria was mean ADSI score of ≥ 6 and ≤ 12)**
  2. **<u>Higher ADSI scores at baseline correlated with improved overall treatment effect separation of FMX114 vs. vehicle</u>**
- ✓ **Review of full data set including subanalyses support potential progression of FMX114 program**
- ✓ **FMX114 is Phase 2b ready**

VYNE™ THERAPEUTICS

Phase 2b Study Design Applies Key Learnings from Phase 2a:

Phase 2a	Key Learnings & Rationale	Phase 2b
• 2-arm double-blind intra-lesional design with patient acting as self-control with 2 lesions of similar size and severity	• Eliminate risk of patients using active drug on lesions assigned to vehicle	• Conventional 4-arm double blind design (pivotal enabling)
• Active Drug: tofacitinib 0.6% + fingolimod 0.01%	• Safety and PK data from P1b/2a support increased concentration of S1P1 3-fold to improve potential effect of combination drug	• Active Drug: tofacitinib 0.6% + fingolimod 0.03%
• Dosing BID		• Dosing BID
• N=21 patients (42 lesions)	• Larger patient study size improves statistical powering	• N=200 patients (50 patients per arm)
• Primary efficacy endpoint is ADSI score at week 4	• EASI score is a widely used efficacy measurement for AD studies • Continued improvement of efficacy results observed beyond 4 weeks of treatment in P1b/2a	• Primary efficacy endpoint is absolute change in EASI score at week 6
• Enrolled patients with mild-to-moderate disease with target lesion ADSI baseline severity range ≥ 6 ≤ 12	• Higher baseline disease severity scores (i.e., more severe disease) correlated with improved overall treatment effect separation of FMX114 vs. vehicle in P1b/2a subanalyses	• Enroll patients with moderate-to-severe disease (defined as EASI score 7>to<50) with baseline EASI severity score between 10>to<49
• Study initiated in Australia & completed in U.S.	• Enhance operational oversight and clinical trial execution	• North American sites only

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