Treating Systemic Lupus Erythematosus: How QSP Can Support Drug Development & Clinical Trial Design

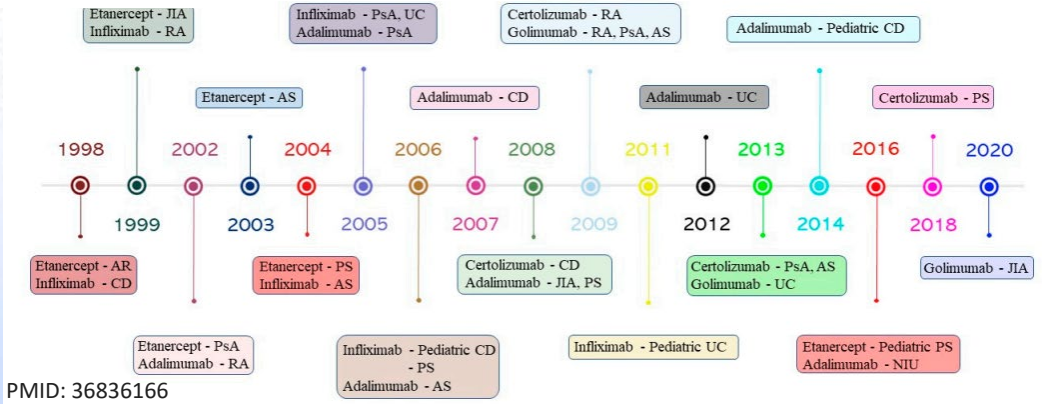
June 27, 2024

Disclaimer: DILIsym Services are developed and provided as an educational tool based on assessment of the current scientific and clinical information, and accepted approaches for drug safety and efficacy. The resultant data, suggestions, and conclusions ("Guidelines") should not be considered inclusive of all proper approaches or methods, and they cannot guarantee any specific outcome, nor establish a standard of care. These Guidelines are not intended to dictate the treatment of any particular patient. Patient care and treatment decisions should always be based on the independent medical judgment of health care providers, given each patient's individual clinical circumstances.

SLE: An Unmet Need

- Autoimmune conditions have seen an explosion in success of biologic therapies
- SLE has lagged behind in the benefit of biologics → Why?
- SLP's tools in quantitative systems pharmacology modeling to understand SLE and guide clinical trial design

Anti-TNFs in Arthritis



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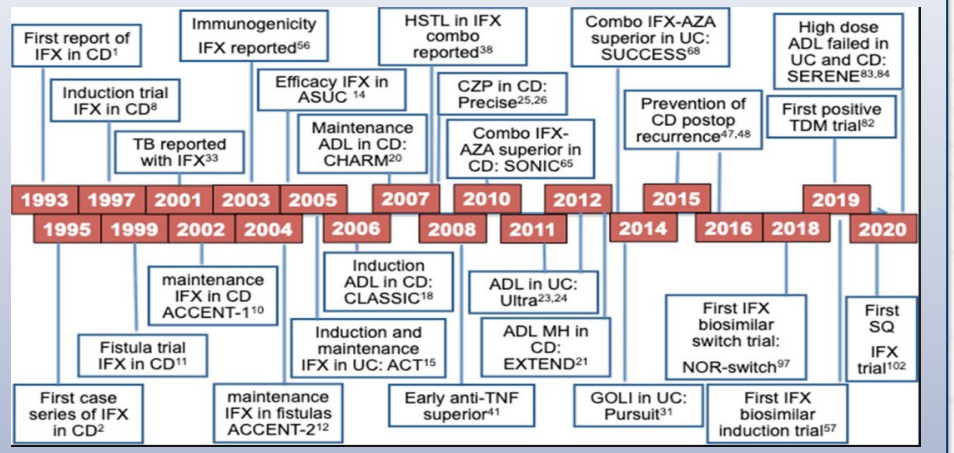
Anti-TNFs in IBD



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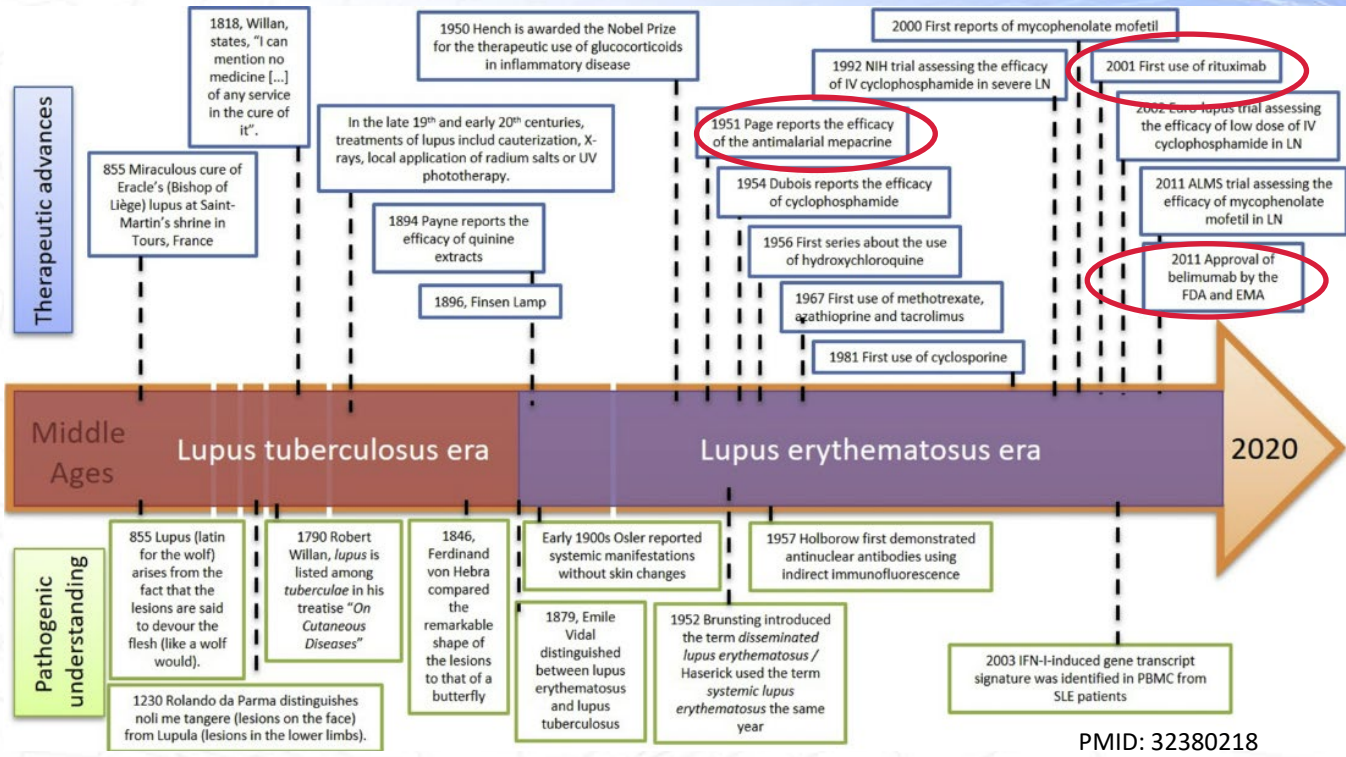
Systemic Lupus Erythematosus



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Anifrolumab approved by FDA in **2021** and EMA in **2022**

Who We Are

NASDAQ: SLP

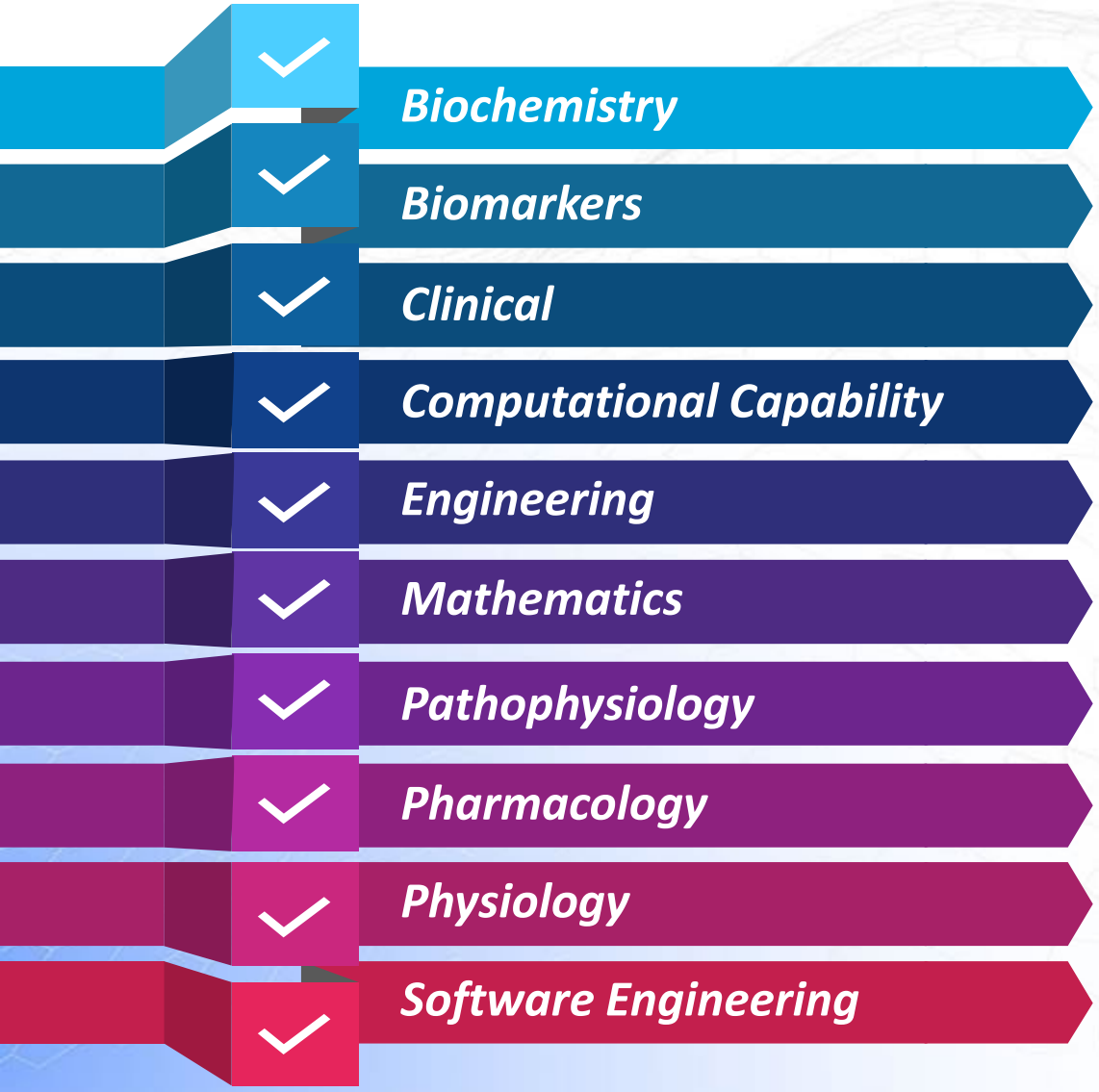
- **Cheminformatics**
  Software & Services
- **PBPK**
  Software & Services
- **Quantitative Systems Pharmacology (QSP)**
  Software & Services
- **Clinical Pharmacology & Pharmacometrics (CPP)**
  Software & Services
- **Regulatory Strategies**
  Services

190+
Employees Worldwide

>25 yrs.
Established In 1996

>280 Pharmaceutical, biotechnology, chemicals, cosmetics, and consumer goods companies in the U.S., Europe, Asia, and South America

QSP Modeling at Simulations Plus Is A Multi-Disciplinary Effort



- Simulations Plus QSP group's technical staff includes 35 modelers
- Expertise in pathophysiological, clinical, and pharmacologic aspects of treating numerous diseases
- Wide array of training and backgrounds coming together to achieve multidisciplinary goals
- Tremendous amount of collective QSP modeling experience including several original pioneers of the discipline
- Superlative communication skills across team
- Emphasis on collaborative approach

Simulations Plus Has A Growing Library of Existing QSP and QST Models to Address Your Questions

QSP: Inflammatory and Fibrotic Diseases

- Non-alcoholic fatty liver disease / steatohepatitis (NAFLD/NASH)
- Idiopathic pulmonary fibrosis (IPF)
- Interstitial lung disease (ILD) associated with systemic sclerosis
- Wound healing after myocardial infarction (MI)
- Uric acid disposition in gout
- Dysregulation of alternative and terminal pathways (AP, TP) of complement

QSP: Metabolic Diseases

- Obesity

QST: Liver and Kidney Safety

- Drug induced liver injury (DILI)
- Drug induced acute kidney injury

QSP: Immuno-Oncology

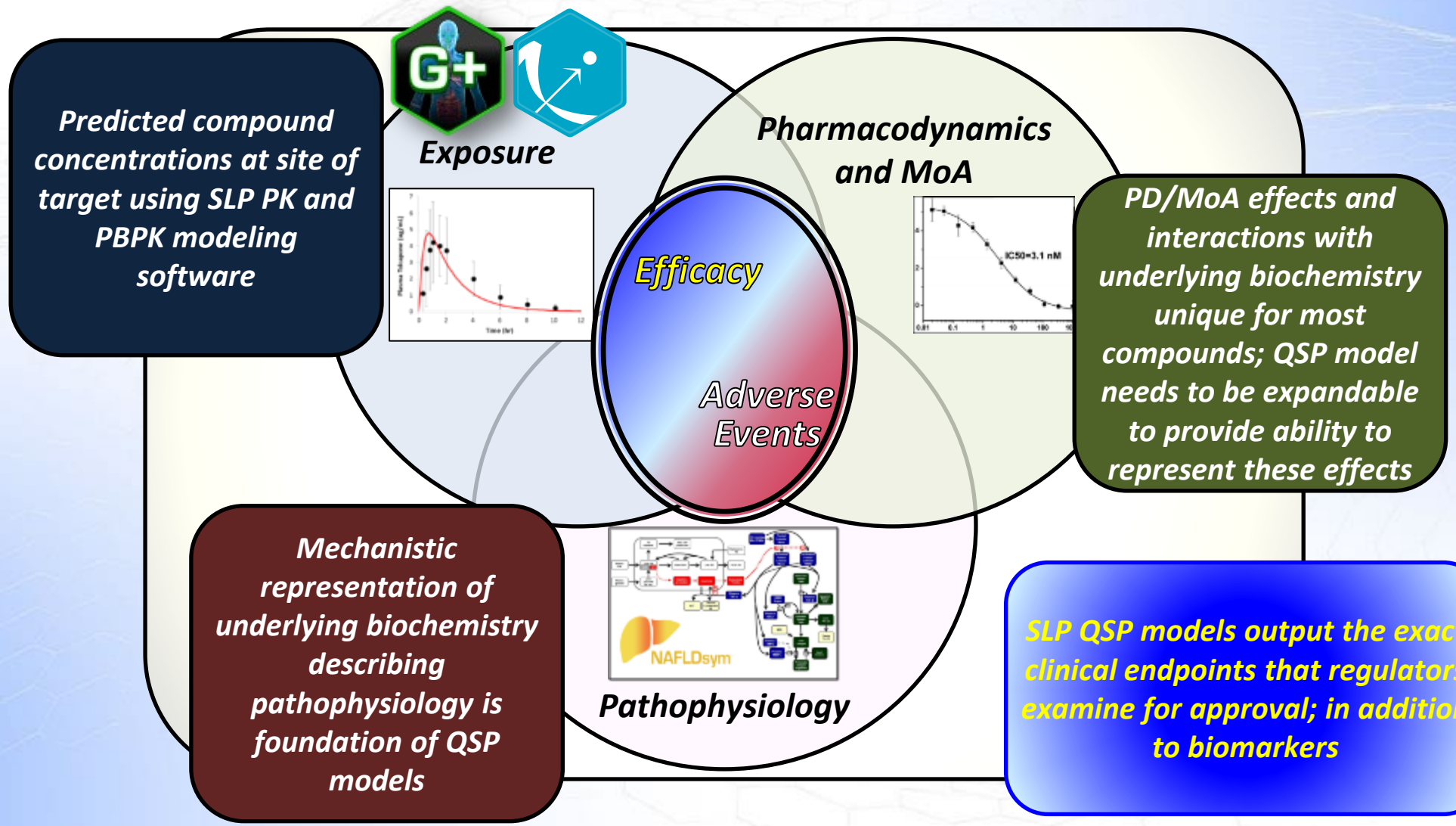
- Acute myeloid leukemia (AML)
- Multiple myeloma (MM)
- Solid tumor (NSCLC, melanoma, prostate cancer, colorectal cancer, ovarian cancer*, endometrial*)
- Diffuse large B-cell lymphoma (DLBCL)

QSP: Autoimmune Diseases

- Rheumatoid arthritis (RA)
- Psoriatic arthritis (PSA)
- Psoriasis (PSO)
- Atopic dermatitis (AD)
- Systemic lupus erythematosus (SLE including CLE)
- Dermatomyositis
- Ulcerative colitis (UC)
- Crohn's disease (CD)
- Asthma* and COPD*

**under development*

QSP Models Predict Efficacy via the Intersection Between Pathophysiology Mechanisms, Compound Exposure, and PD



THALES

An integrated system for all stages of model development: *model design, implementation, fitting, debugging, analysis, prediction*

Top-Down Design

Encourages top-down, incremental design, folding in detail only when necessary

Simultaneous Fitting

Supports simultaneous fitting to data at many levels

Population Generation

Virtual patient population generation is incorporated into the fitting pipeline

Reaction Operator

Users write models in higher-level reaction operators & generate lower-level equations

Efficient Simulation

Simulation & analysis is automatically distributed either in the cloud or on the Simulations Plus cluster

Complex Simulation Pipeline

Supports complex, conditional simulation workflows for modeling real-world protocols

(e.g. running many trial arms, stopping treatment, switching treatments, etc.)

Automated Documentation

Network diagram, results, & fit/prediction performance are automatically generated

Simulation Results

Detailed simulation results are collected and available for post-hoc analysis

Clinically-relevant modeling

Virtual representation of clinical information provides deeper insight into trial design

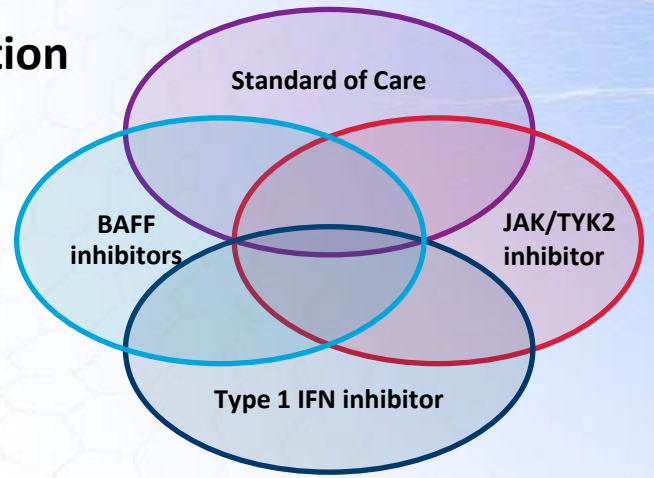
Most often, Simulations Plus' QSP models are used for prediction of trials involving a broad class of patients

- Fitting individual trials is insufficient for predicting response to novel therapeutics
- The models are simultaneously **fitted to all relevant phase 2/3 drug trials and clinical results** to constrain our repertoire of models

Our models are built to include both the necessary biology and clinical details

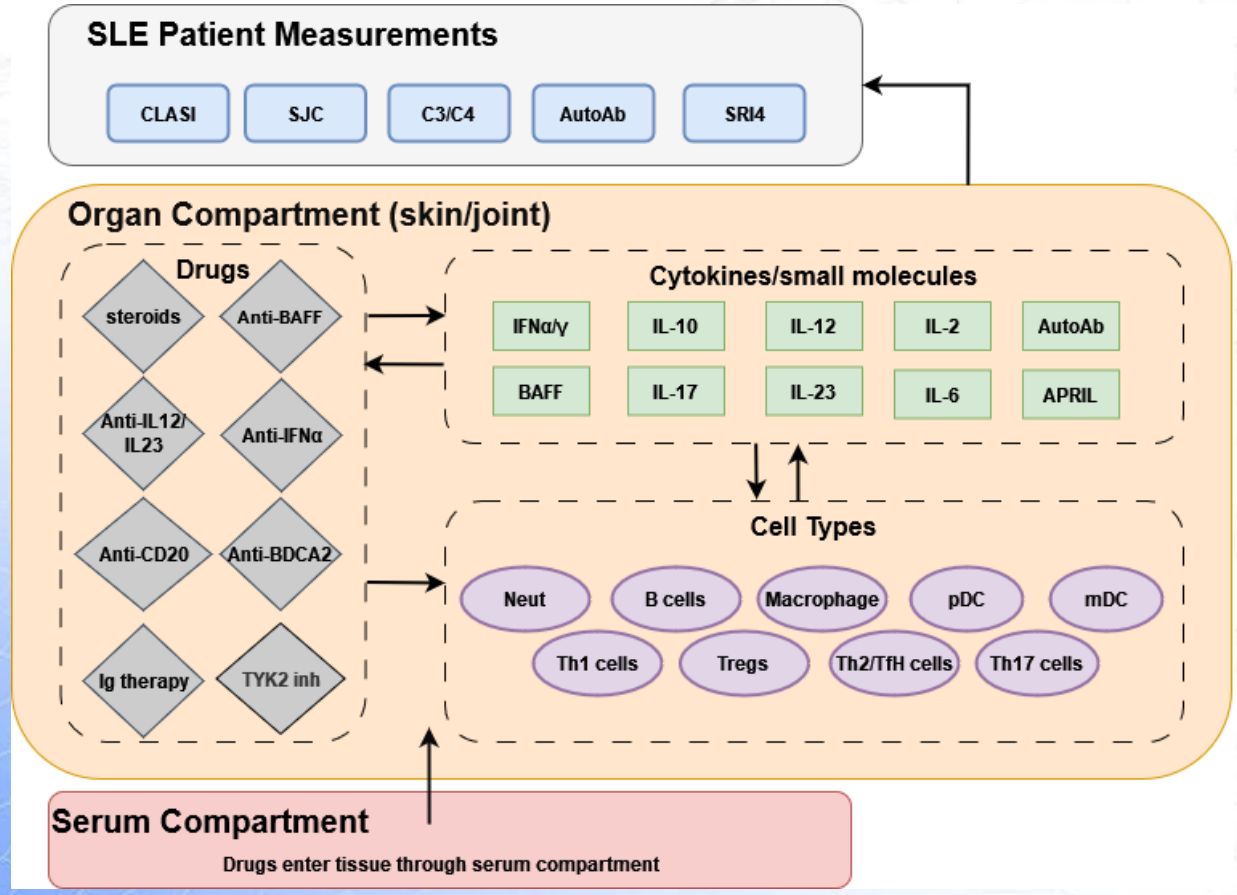
- Outputs are not limited to biological readouts, but instead extend to **clinically-relevant endpoints** used for regulatory decision-making
  - Response criteria and disease activity indices are regularly included in our models
- In addition to inclusion of aggregate clinical data our models **directly represent protocols relevant for trial design**
  - Inclusion/exclusion criteria
  - Usage of concomitant medications
  - Requirements of prior lines of therapy
  - Washout periods

SLE population



Disease	# of Trials	# Constraints	# Clinical Endpoints
Multiple myeloma	31	811	11
NSCLC	27	1355	8
Crohn's disease	33	938	12
SLE	29	1261	8
Psoriasis	32	1375	7
Rheumatoid arthritis	61	5587	11

Systemic lupus erythematosus (SLE)



- SLE is an auto-immune condition that involves up to 9 organ systems
  - Multiple organ involvement is a contributor to slower treatment development
  - SLP's model includes the sites of primary activity utilized in evaluating tissue-specific disease activity: skin and joints
- First approved biologic, belimumab, was approved after additional analysis identified patients with higher musculoskeletal and mucocutaneous disease activity showed the most improvement with belimumab
  - Manzi 2012 post-hoc analysis of belimumab (PMID: 22550315)
- More recently, organ-specific endpoint like CLASI and SJC are reported in additional to general SLE endpoints

SLE Response Criteria: Which endpoint?

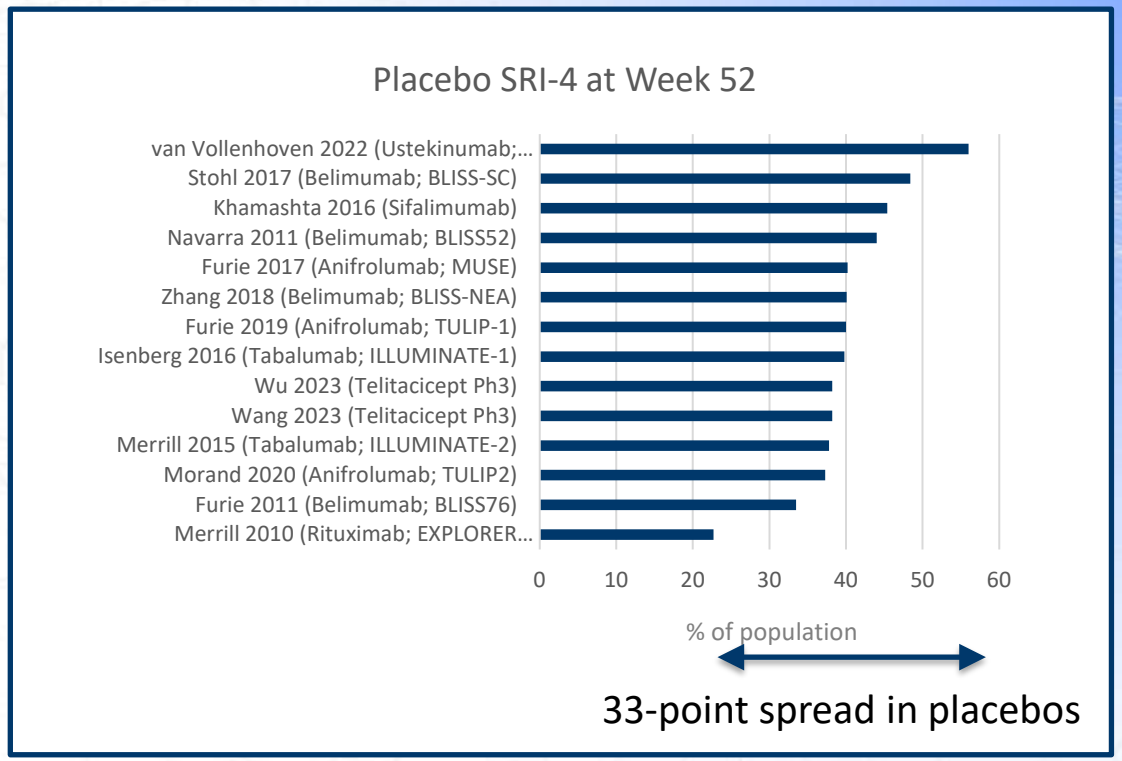
Response criteria	Model Definition
SRI4	A 4 point decrease in the SLEDAI score from baseline, AND no worsening in BILAG AND no worsening in PGA
BICLA*	Meeting both of the following criteria: • All BILAG A scores at baseline improve to B/C/D, and all B scores at baseline improve to C/D. • No new BILAG A or no more than 1 new B score • No worsening of SLEDAI from baseline
LLDAS*	Meeting both of the following criteria: • SLEDAI <=4 • No new lupus disease activity • Current prednisolone dose <=7.5 mg daily
CLASI -50	>=50% reduction in CLASI score in patients with CLASI >=10 at baseline
CLASI Score	Measurement of skin symptoms
SLEDAI*	Disease activity score
SJC	Number of swollen joints
TJC (when available)	Number of tender joints
Steroid tapering protocols	• Optional vs required tapering • Tapering is sometimes included in combination with other endpoints

* Requires individual patient data

- Of the listed endpoints in this table, joint counts (TJC, SJC) and CLASI-based endpoints are the most accessible for direct modeling
- Our model can leverage proprietary individual patient data in order to better predict composite disease activity scores

SLE Trial Designs and Placebo Variability

- SLE trials are more complex than those for other auto-immune conditions
  - Required/optional steroid taper protocols
  - Mean & maximum steroid dose
- Consequence:
  - SRI4 had a 30% spread in placebos
  - Difference between treatment and placebo was 10% on average
- Other considerations
  - Inclusion/exclusion criteria are more variable. Specifically, newer trials exclude patients with certain feature
  - Neurological lupus and lupus nephritis have their own trials (and endpoints)
- Hypothesis that breaking placebos out by trial design would improve detection of differences between placebos and treatments
  - To address this, the SLE model has ***6 separate placebos***



SLE Patient Pipeline

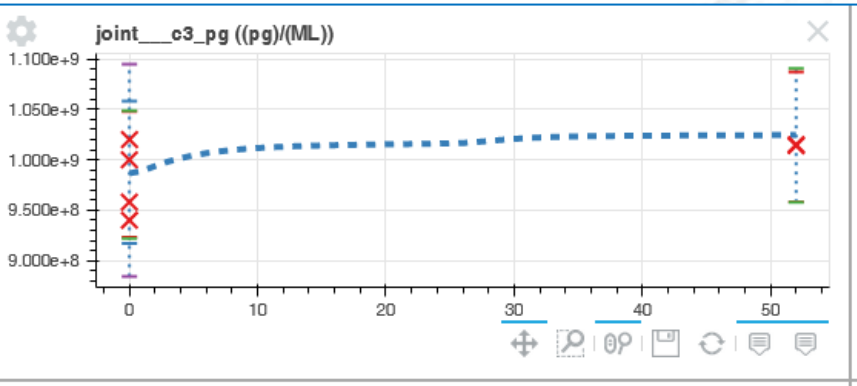
- **Patient Pipeline**: Virtual patients are generated and optimized while being simulated through a pipeline of scenarios
- **Standard of Care:** 7.5mg steroids and an anti-malarials
- **Steroid ramp-up:** prepares patients for trials by increasing and/or decreasing their steroids as needed based on their symptoms until they have steady disease.
- The final level is **the trials**, all of which occur in parallel.
  - Patients are sorted into all groups for which they are eligible.
  - Each group has its own placebo, allowing for accurate placebo-to-drug deltas.

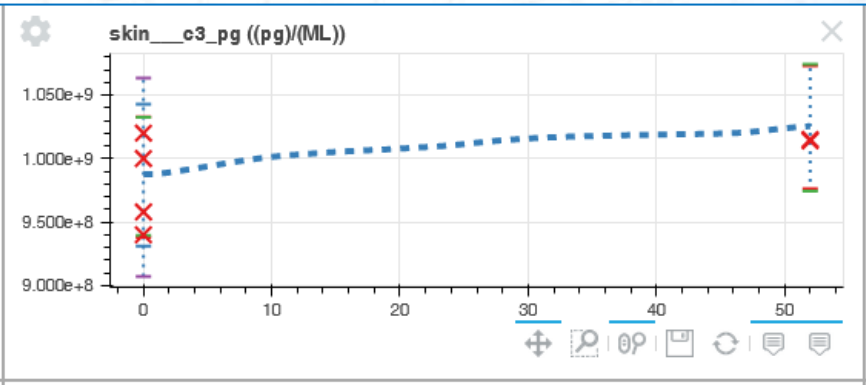
Supported Clinical Trials (license ready)

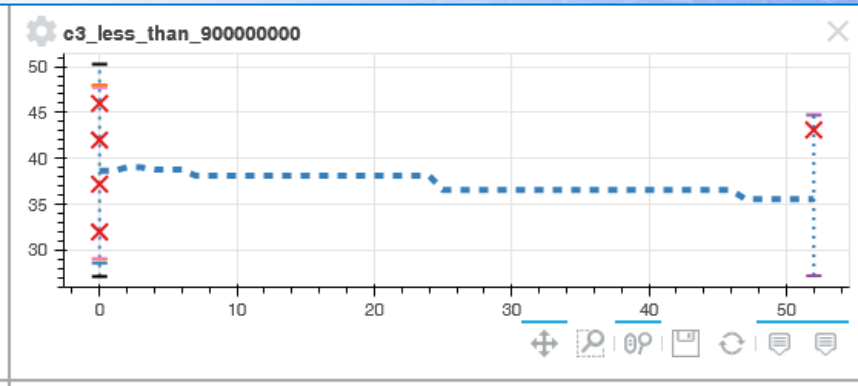
DRUG	MOA	TRIAL	SJC	CLASI	SRI4
Anifrolumab	Anti-IFNR	Furie 2017 (MUSE)	Y	Y	Y
		Furie 2019 (TULIP-1)	Y	Y	Y
		Morand 2020 (TULIP-2)	Y	Y	Y
Atacicept	Anti-BAFF/APRIL	Merrill 2018 (Atacicept)			Y
Belimumab	Anti-BAFF	Navarra 2011 (BLISS52)			Y
		Furie 2011 (BLISS76)			Y
		Stohl 2017 (BLISS-SC)			Y
		Zhang 2018 (BLISS-NEA)			Y
Deucravacitinib	Tyk2 inhibitor	Morand 2023 (PAISLEY)	Y	Y	Y
Epratuzumab	Anti-CD22	Clowse 2017 (EMBODY 1 AND 2)			Y
Ianalumab	Anti-BAFFR	Shen 2023 & Cortes-Hernandez 2023			Y
IVIg		Ky 2015 (CLE trial)		Y	
Lanraplenib	SYK inhibitor	Werth 2022 (CLE trial)		Y	
Litifilimab (BIIB059)	Anti-BDCA2	Furie 2019		Y	
		Werth 2022 (CLE trial) (LILAC)		Y	
		Furie 2022 (LILAC)	Y	Y	Y
Rituximab	Anti-CD20	Merrill 2010 (EXPLORER postHOC)			Y
Sifalimumab	Anti-IFNa	Khamashta 2016	Y	Y	Y
Tabalumab	Anti-BAFF	Isenberg 2016 (ILLUMINATE-1)			Y
		Merrill 2015 (ILLUMINATE-2)			Y
Telitacicept	Anti-BAFF/APRIL	Wu 2019/2023 (phase 2)			Y
		Wang 2023 (phase 3)			Y
Ustekinumab	Anti-IL12/23	Van Vollenhoven 2018	Y	Y	Y
		Van Vollenhoven 2022 (LOTUS)		Y	Y

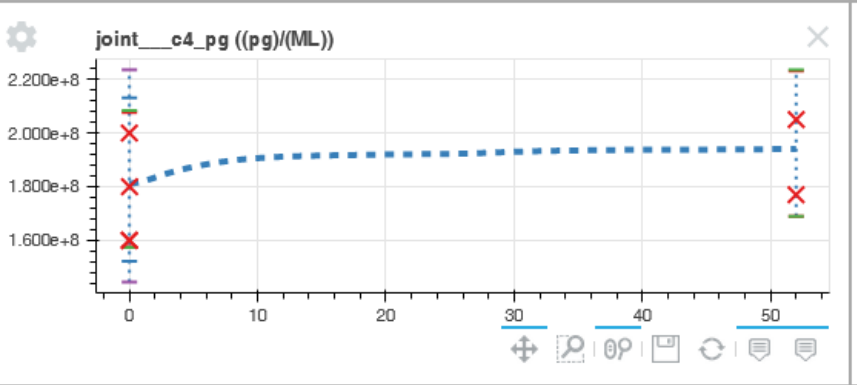
- **Scope of data** scored during virtual patient generation/optimization (across fit/validation):
- **1261 mean constraints**
  - **45 Trials**: Includes standard of care reports (not listed in table) in addition to drug trials
  - **29 Arms**: Does not double count arms run in multiple trials
  - **87 Analytes**: This does not double count for analytes considered in delta-from-placebo form, nor for those assessed with different subgroupings
- Additional model rules
  - Heuristics on biomarker ranges and patient type percentages
  - Flare distributions/frequencies
- Further unscored literature-based constraints
  - Patient parameter ranges
  - Patient-classification thresholds (e.g. IFNgs-High)
  - Compartment relationships
  - SRI-4 Predictor

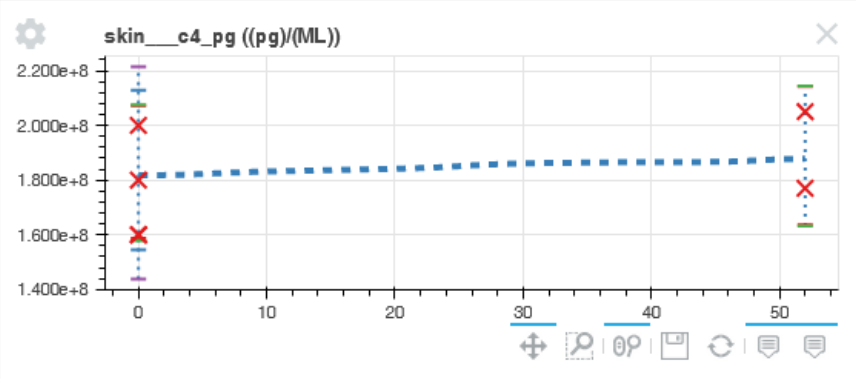
Model Training: Placebo (without steroid taper)

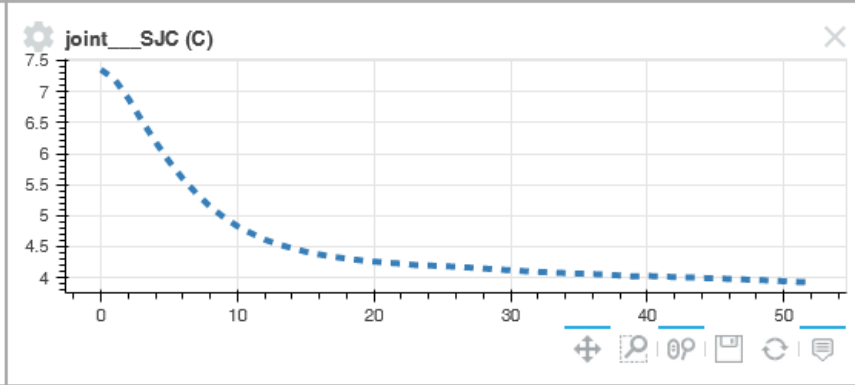


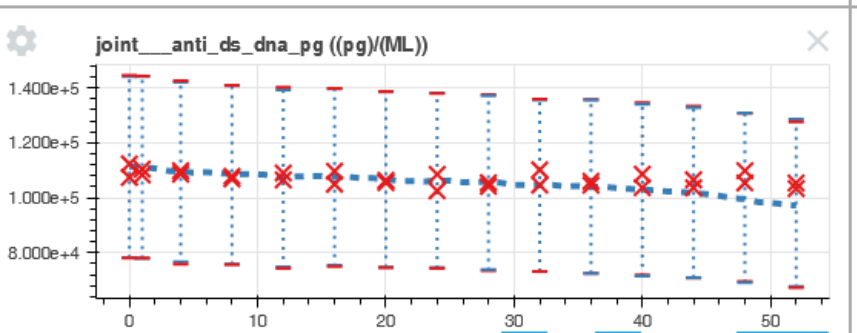


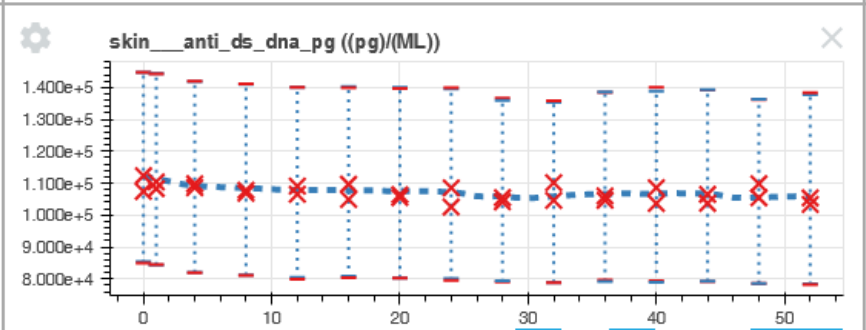


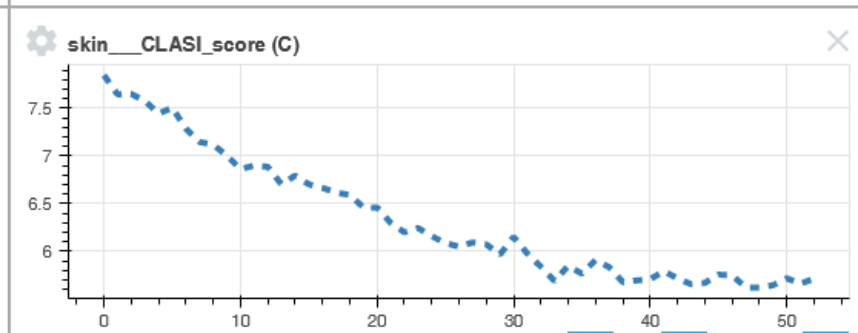




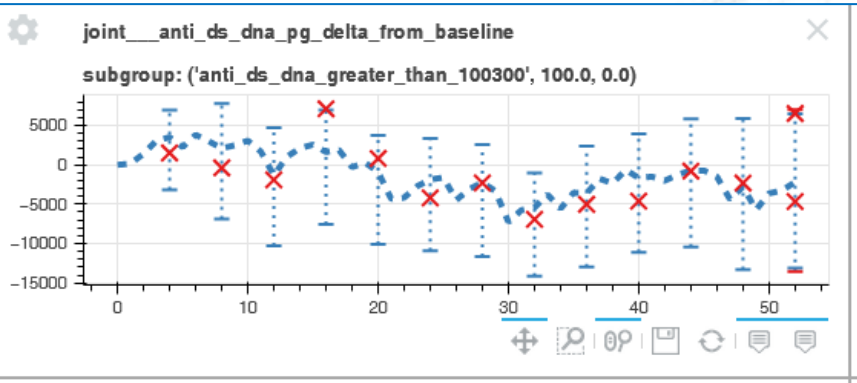


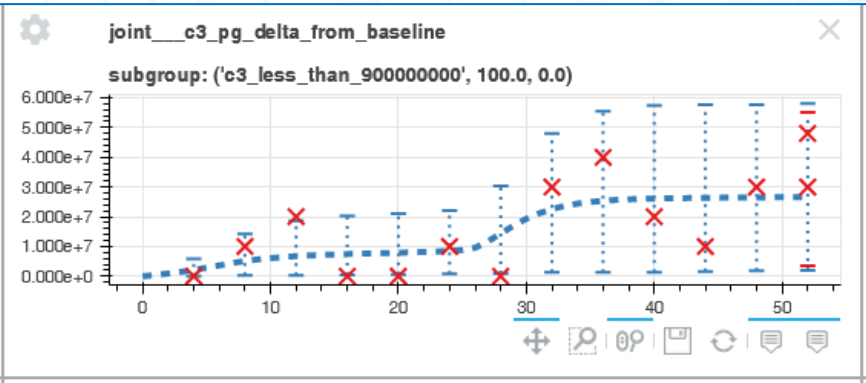


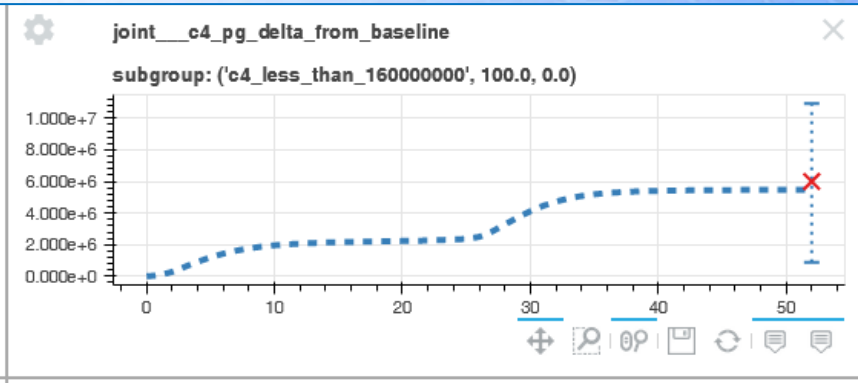


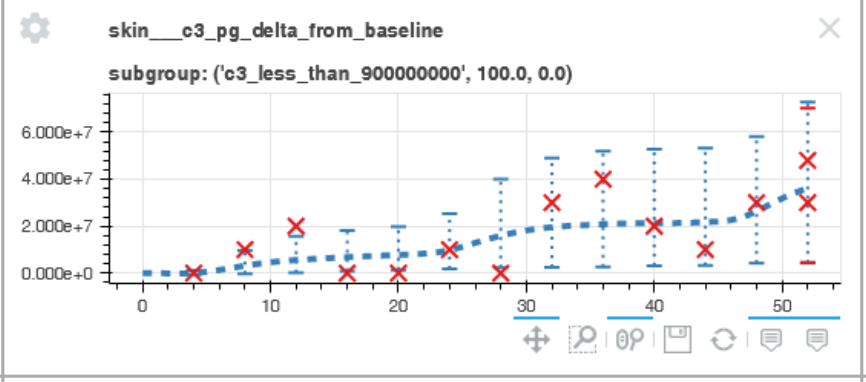


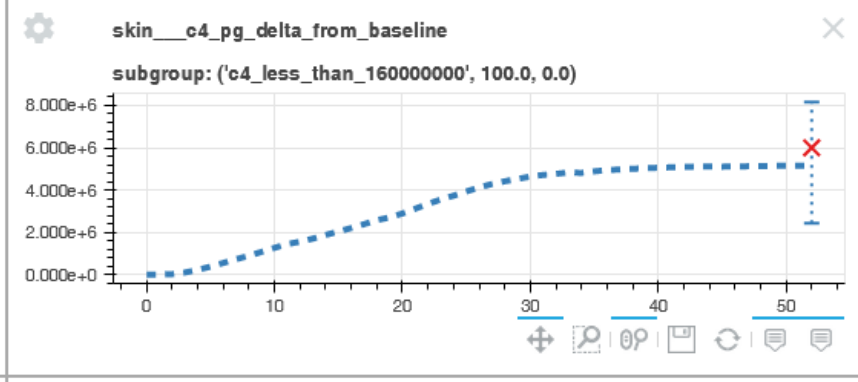
Model Training: Placebo (with steroid taper)

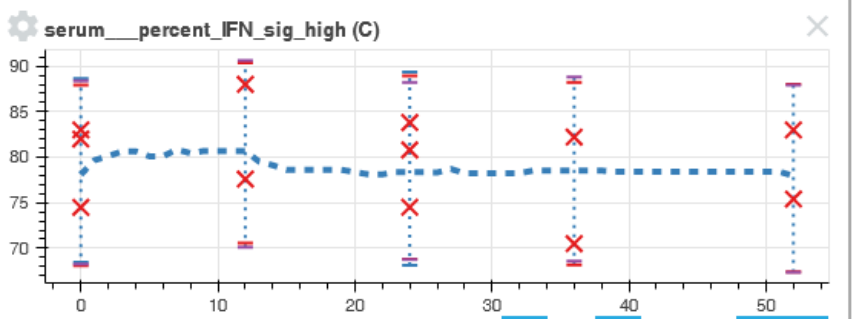


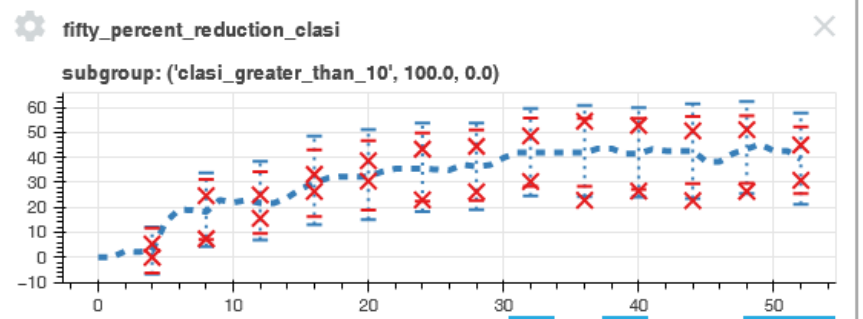


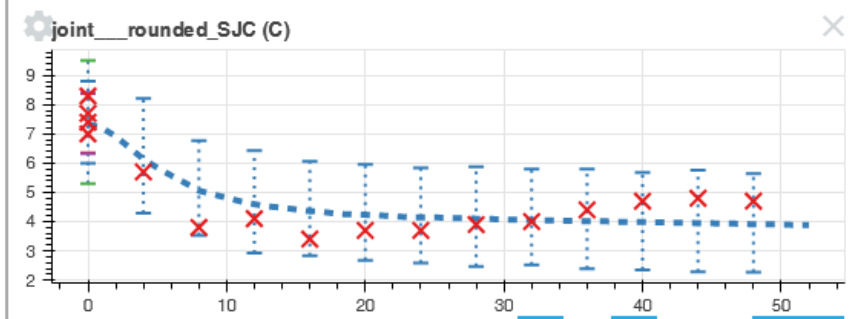




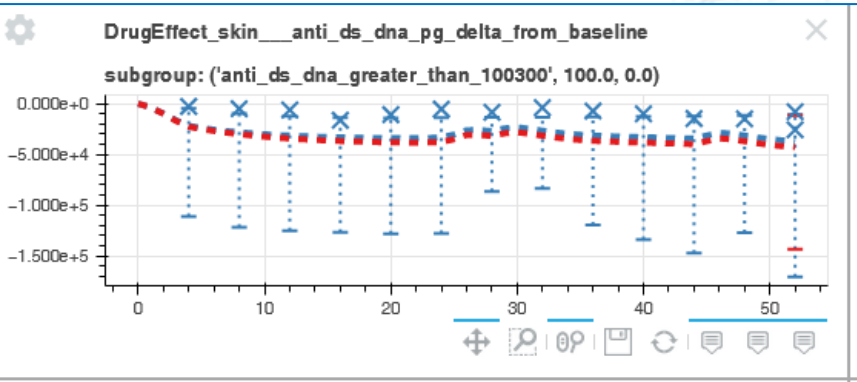


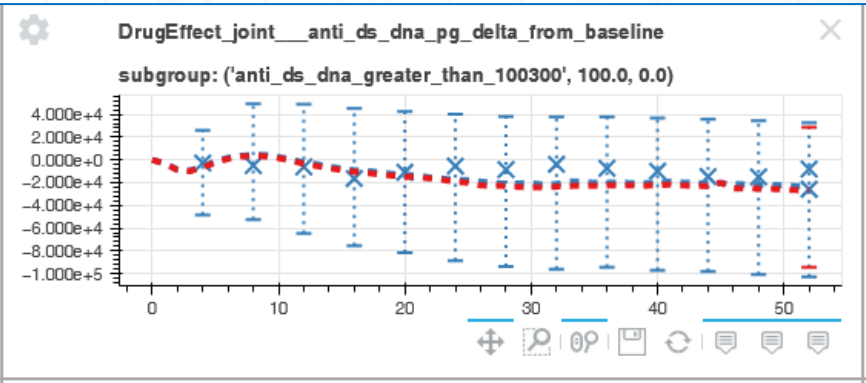


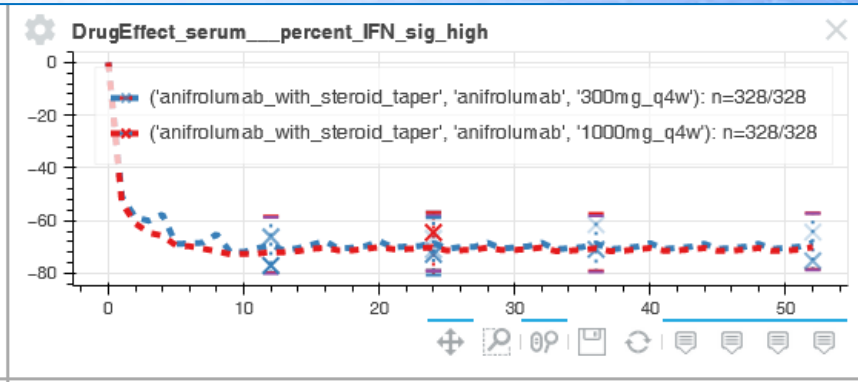


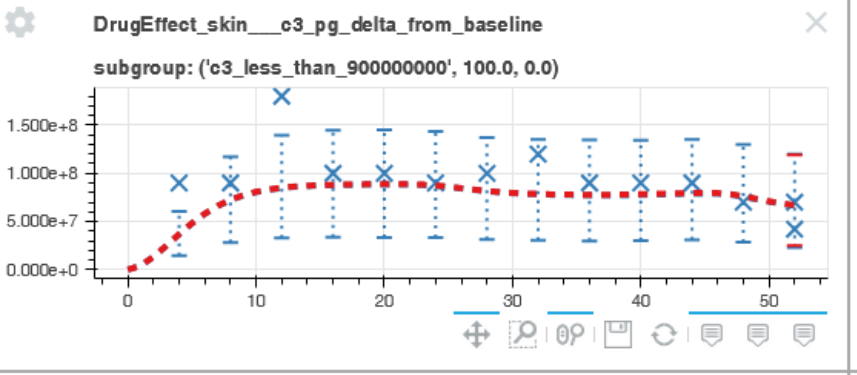


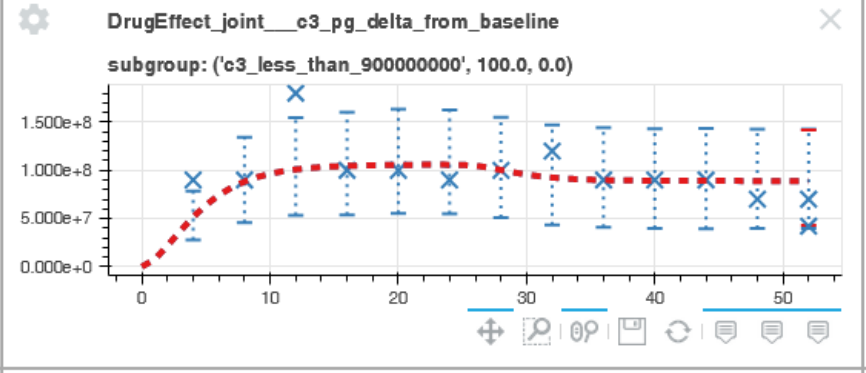
Model Training: Anifrolumab

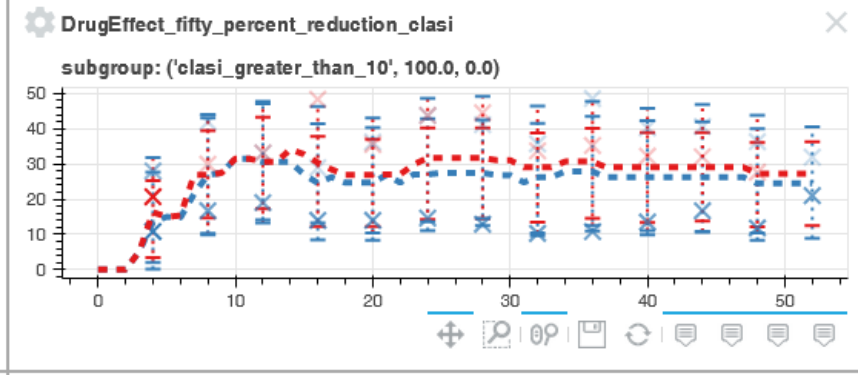


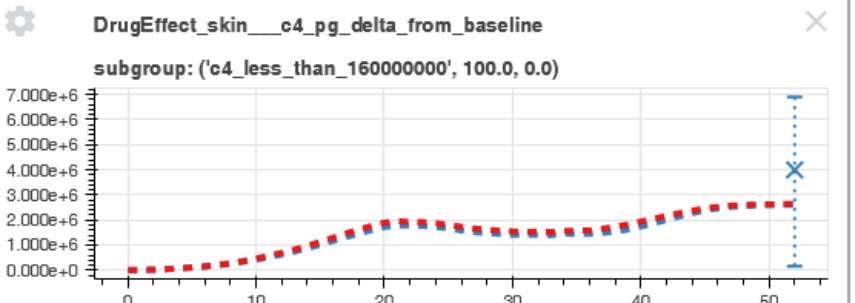


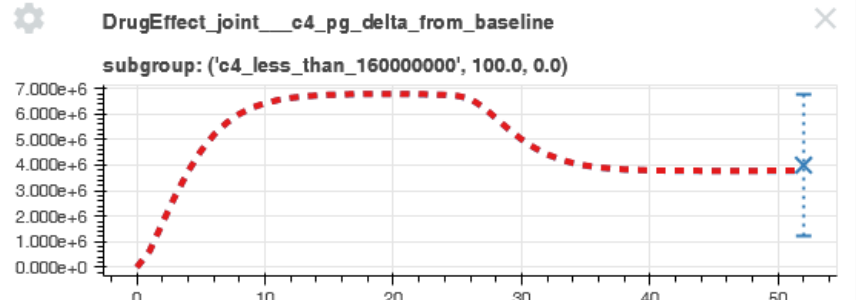


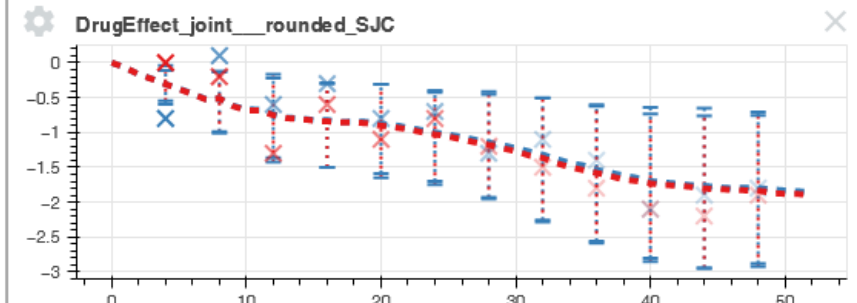












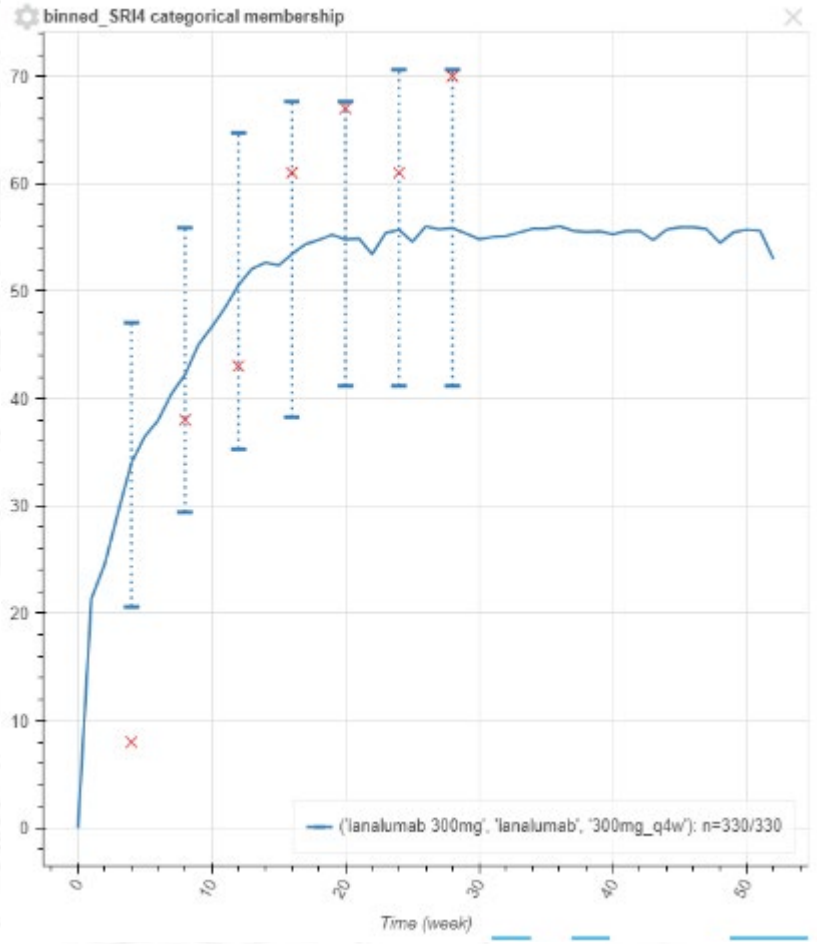
Model Performance - Validation

- Model is built using in vitro data to inform lower-level biology, then fit to published clinical trial data
  - >1000 clinical data points in license ready model
  - Using proprietary individual patient data, model can be fit to ~4000 published data points (in addition to the individual data).
  - *Note*: Fitting strategy is customized based on project

- Monitor Fitting & Validation
  - Visual assessments
  - Quantitative assessments: calculate the percentage of datapoints that fall within the model confidence intervals (fit quality ranges from 70-90% of data points falling within the model confidence intervals, depending on the type of data)

Prediction: Ianalumab (anti-BAFF receptor)

Model was informed of drug mechanism, but was NOT informed of clinical efficacy



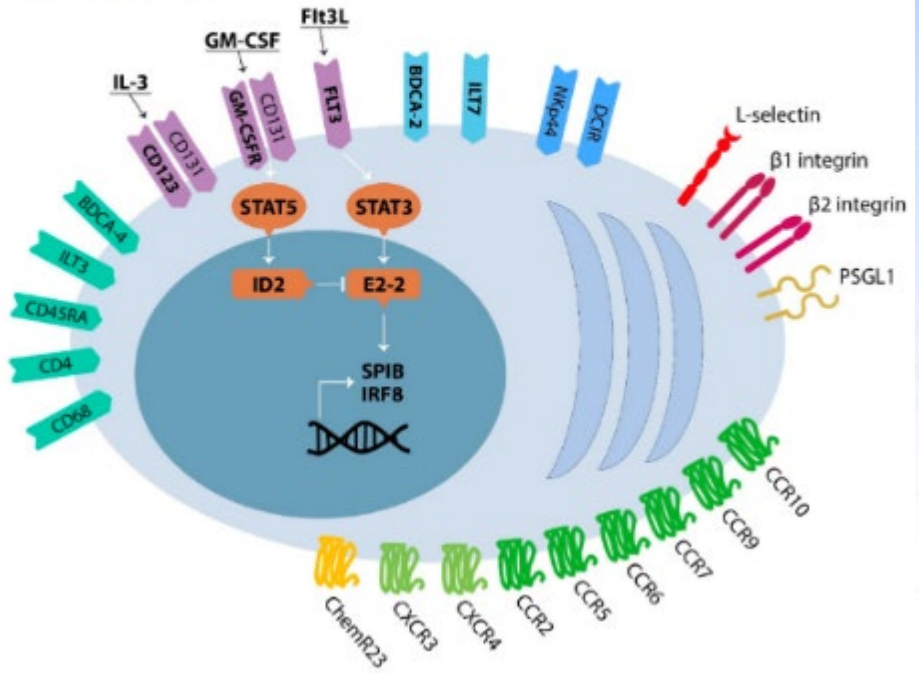
pDC targeting drugs

Litifilimab vs Daxdilimab

Plasmacytoid Dendritic Cells (pDCs)

- Plasmacytoid dendritic cells (pDCs) are a subset of dendritic cells that play a crucial role in SLE
  - Type I IFN production
  - Antigen Presentation
  - B cell activation
  - TLR7/9 activation
- Therapies emerging to target pDCs

Figure 1. The phenotype of human pDCs. Graphical representation of the phenotype of a human pDC. Human pDCs express a broad range of surface antigens, adhesion molecules and chemotactic receptors. Among these, the surface receptors BDCA-2 and ILT7 are selectively express by human pDCs. Moreover, Flt3, GM-CSFR, and CD123 regulate the pDC development, homeostasis and survival via the ID2 and E2-2 transcription factors.



A Tale of Two Therapies…

Horizon's (HZNP) Daxdilimab Fails to Meet Goal in Lupus Study

Zacks via Yahoo Finance · 9 months ago

Horizon Therapeutics plc HZNP announced the failure of the phase II study evaluating **daxdilimab** for...

WHY???

The NEW ENGLAND JOURNAL of MEDICINE

SPECIALTIES TOPICS MULTIMEDIA CURRENT ISSUE LEARNING/CME AUTHOR CENTER PUBLICATIONS

ORIGINAL ARTICLE

Trial of Anti-BDCA2 Antibody Litifilimab for Cutaneous Lupus Erythematosus

Authors: Victoria P. Werth, M.D., Richard A. Furie, M.D., Juanita Romero-Diaz, M.D., Sandra Navarra, M.D., Kenneth Kalunian, M.D., Ronald F. van Vollenhoven, M.D., Filippa Nyberg, M.D., +12, for the LILAC Trial Investigators° Author Info & Affiliations

CONCLUSIONS

In a phase 2 trial involving participants with cutaneous lupus erythematosus, treatment with litifilimab was superior to placebo with regard to a measure of skin disease activity over a period of 16 weeks. Larger and longer trials are needed to determine the effect and safety of litifilimab for the treatment of cutaneous lupus erythematosus. (Funded by Biogen; LILAC ClinicalTrials.gov number, NCT02847598.)

SimulationsPlus

SLE: Patient Populations and Endpoints

	VIB7734 (Viela Bio)	BIIB059
Drug Name	Daxdilimab	Litifilimab
Target	ILT7	BDCA-2
Trial NCT	NCT04925934 (Ph2)	NCT02106897 (PK) NCT02847598 (Ph2)
Population	Standard general SLE criteria, excluding LN and neuro	CLE w or w/out SLE
Primary Endpoints	% of Participants who achieve BICLA ***and*** OGC (oral glucocorticoid) reduction response at Week 48	SJC & CLASI-A at Week 16
Secondary Endpoints	CLASI-50 in pats CLASI-A≥10 SRI4+OGC ≤7.5mg LLDAS % pats w/ baseline OCG ≥10 who achieve ≤7.5mg	CLASI-50 @ Wk 12 & 16 % Change in CLASI Various point changes in CLASI (many more)

Both Phase 2 trials

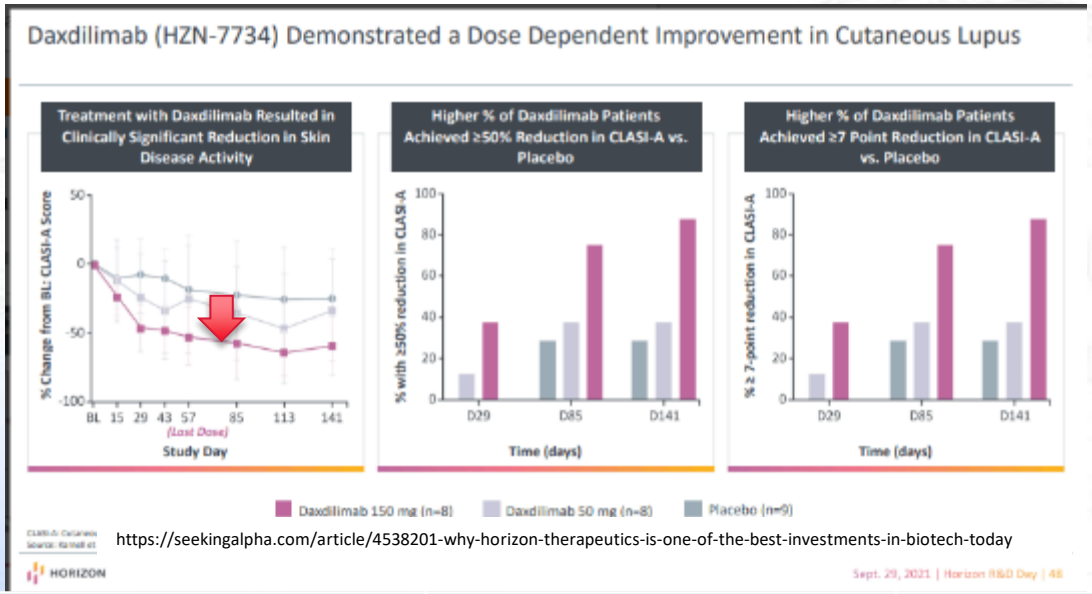
Different patient population

Different clinical endpoints

Both assessed CLASI-A and CLASI-50

Comparing Apples to Apples: CLASI-A and CLASI-50

Daxdilimab



https://seekingalpha.com/article/4538201-why-horizon-therapeutics-is-one-of-the-best-investments-in-biotech-today

Day 85 ~ Wk 12
Day 113 ~ Wk 16

Litifilimab

Werth 2022, PMID: 35939578

Table 2. Primary and Secondary Efficacy End Points at Weeks 12 and 16.*

End Point	Litifilimab, 50 mg (N=26)	Litifilimab, 150 mg (N=25)	Litifilimab, 450 mg (N=48)	Placebo (N=33)
Primary				
Percent change from baseline in CLASI-A score at wk 16				
LSM change — %	−38.8±7.5	−47.9±7.5	−42.5±5.5	−14.5±6.4
LSM difference vs. placebo (95% CI) — percentage points	−24.3 (−43.7 to −4.9)	−33.4 (−52.7 to −14.1)	−28.0 (−44.6 to −11.4)	
Secondary				
CLASI-50 response: decrease of ≥50% from baseline in CLASI-A score				
At wk 12				
No. of participants (%)	10 (38)	12 (48)	18 (38)	4 (12)
LSM — %	42.3±9.5	51.2±10.6	39.4±7.6	16.6±5.9
LSM difference vs. placebo (95% CI) — percentage points	25.7 (5.1 to 46.2)	34.6 (12.0 to 57.1)	22.8 (5.2 to 40.4)	
At wk 16				
No. of participants/total no. (%)	10/26 (38)	11/25 (44)	20/43 (47)	7/32 (22)
LSM — %	41.4±9.9	46.8±10.5	48.9±8.1	25.6±7.6
LSM difference vs. placebo (95% CI) — percentage points	15.8 (−7.2 to 38.8)	21.2 (−2.8 to 45.2)	23.3 (2.9 to 43.6)	
Percent change from baseline in CLASI-A score at wk 12				
LSM change — %	−41.8±7.1	−48.6±7.1	−37.5±5.2	−11.5±6.1
LSM difference vs. placebo (95% CI) — percentage points	−30.4 (−48.8 to −12.0)	−37.2 (−55.5 to −18.9)	−26.1 (−41.7 to −10.4)	

	Daxdilimab (DISCONTINUED)	Litifilimab (in development)
% Change in CLASI-A @ wk 12	PBO: -22.2% 50mg: -35.7% 150mg: -57.7%	PBO: -11.5% 50mg: -41.8% 150mg: -48.6% 450mg: -37.5%
% Change in CLASI-A @ wk 16	PBO: -26% 50mg: -34.5% 150mg: -60.4%	PBO: -14.5% 50mg: -38.8% 150mg: -47.9% 450mg: -42.5%
CLASI-50 @ wk 12	PBO: 28.5% 50mg: 37.7% 150mg: 74.9%	PBO: 12% 50mg: 38% 150mg: 48% 450mg: 38%
CLASI-50 @ wk 16	PBO: 28.3% 50mg: 39.7% 150mg: 87.7%	PBO: 22% 50mg: 38% 150mg: 44% 450mg: 47%

The importance of choosing the right patients and the right endpoint!

Daxdilimab had better efficacy than Litifilimab when comparing the same endpoints

Importance of QSP in Complex Diseases

- SLE is multi-faceted disease that can manifest across many organ systems
  - Multiple clinical endpoints
  - Many patient subpopulations
  - Many different trial designs (entry criteria, steroid protocols)

  - Issues for the trial design are therapy specific:
    - Best steroid protocol (max steroid dose, steroid tapering?)
  - SLP's clinically validated SLE QSP model can assist in designing the optimal trial for a specific therapy by exploring these factors

SimulationsPlus

Questions?