Enrichment, Response Amplification, Separation, and Inclusion: Quantifying Trial Design Trade-offs in SLE with QSP SimPops™ Modeling

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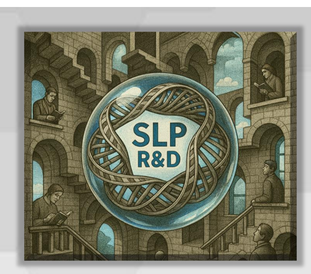

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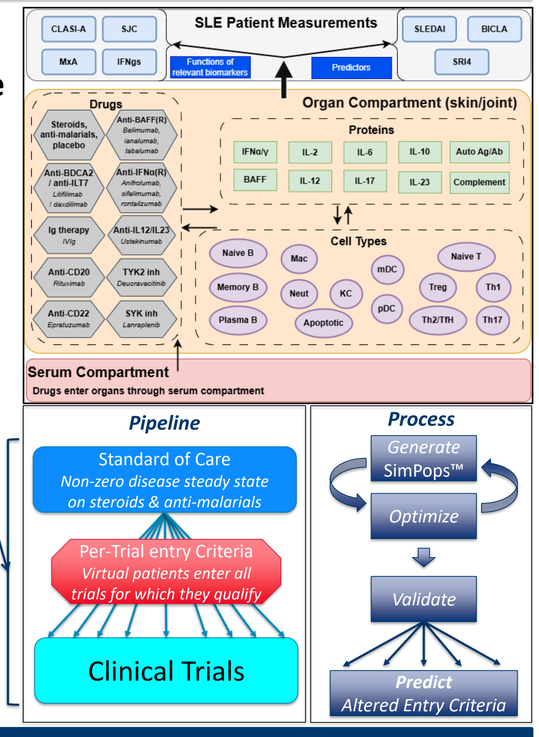
OBJECTIVE

- Systemic lupus erythematosus **(SLE) trials suffer from equivocal or failed trial outcomes**.
- The objective of this work is to use a quantitative systems pharmacology (QSP) model to **establish an analysis framework that characterizes trial outcome trade-offs** stemming from disease heterogeneity and entry criteria.
- This framework aims to improve prediction of treatment response to **inform trial design and precision medicine**.

METHODS

- A SimPops™ cohort is simultaneously generated and optimized using a mechanistically driven **ordinary differential equation (ODE) and machine learning (ML) model of SLE and CLE** (cutaneous lupus erythematosus).
- Key inflammatory biomarkers and pathways underlying **skin and joint disease** link to clinical outcomes within an immunopathology-guided network.
- **Published multimodal clinical trial data and entry criteria** across anifrolumab, belimumab, litifilimab, deucravacitinib, IVIg, lanraplenib, sifalimumab, ustekinumab, daxdilimab, rontalizumab, ianalumab, tabalumab, epratuzumab, rituximab, placebos, and standard of care are used to fit and validate the model.
- Predictions assess binary clinical measures of response and patient inclusion under theoretical additional entry criteria, in the context of the TULIP-2 anifrolumab trial (3).



RESULTS

Key Findings:

- Among enrichment strategies, **SLEDAI_2K ≥ 8 (vs. baseline ≥ 6) provided the most favorable balance between efficacy amplification and cohort retention**.
  - Across endpoints, the composite "sum of deltas" scoring metric used here increased from 161 to 229 while maintaining 67% inclusion.
  - Absolute drug response rates increased across endpoints, suggesting higher predicted probability of response in patients meeting this criterion.
- **CLASI ≥ 8 enrichment substantially amplified SRI-4 and BICLA deltas**,
  - increasing the "sum of deltas" to 214 through SLEDAI_2K-4 / SRI4 / BICLA alone,
    - with the highest sum (80) while excluding CLASI-X analytes.
  - However, inclusion was reduced to 21%.
  - In contrast, imposing baseline SJC ≥ 4 did not enhance SRI-4 or BICLA deltas,
    - suggesting skin severity preferentially enriches these composite responses relative to joint severity.
- Biomarker-based enrichment (anti-dsDNA, C3, C4) consistently increased *absolute* CLASI-X responses, indicating strong linkage between biomarker activity and cutaneous improvement.
  - However, *deltas* were not uniformly enhanced, highlighting that **higher absolute drug response does not necessarily translate to improved separation between therapy and placebo**.
  - These strategies incurred substantial inclusion trade-offs (7–54% inclusion).

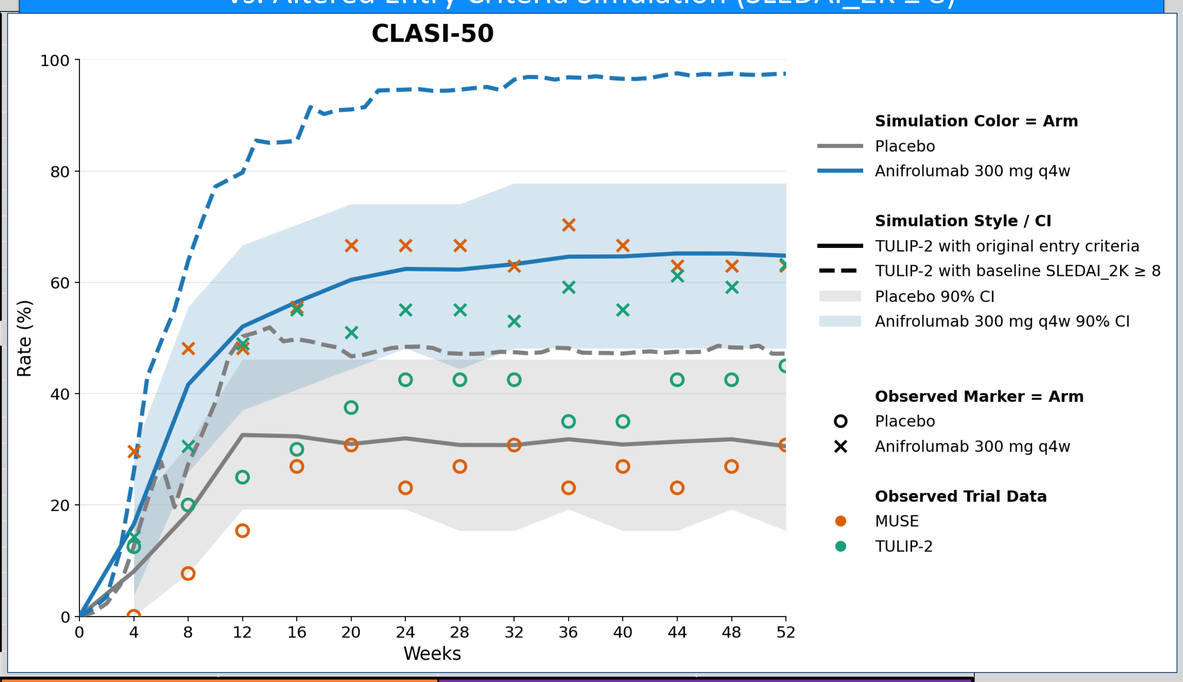
Calibration / Validation:

- 2,294 constraints split across fitting and validation.
- Data includes longitudinal timecourses and discrete endpoints of continuous and binary response analytes, biomarker heuristics, parameter/weight regularizations, and Poisson-distributed flare rates.
- Model performance is summarized as the percentage of mean, median, and binary fitting and validation data points that fall within the 90% credible intervals (CIs) of the model.
  - **70% of fitting data and 60% of validation data are within the model's 90% CIs.**

Extra Entry Criteria — *Beyond TULIP-2 Entry Criteria:* *Steroid ≤ 40 mg/day & SLEDAI_2K ≥ 6*	*Placebo - week 52 **absolutes** - (% achieving response)*						
	Subgroup: Baseline CLASI ≥ 10				*No additional subgroup*		
	CLASI-20	CLASI-50	CLASI-70	CLASI-90	SLEDAI_2K-4	SRI-4	BICLA
High anti_dsDNA (> 100,300 pg/mL)	73	68	44	20	37	54	54
Low C3 (< 9.0e8 pg/mL)	63	54	32	19	30	31	32
Very Low C4 (< 1.0e8 pg/mL)	65	60	56	27	42	61	61
Low C4 (< 1.6e8 pg/mL)	73	69	45	21	41	70	69
SLEDAI_2K ≥ 8	52	47	32	15	50	47	47
CLASI ≥ 8	*Same as original entry criteria because of subgroup*				54	24	25
Swollen Joint Count (SJC) ≥ 4	72	28	3	0	34	72	72
Original TULIP-2 Entry Criteria Only	*54*	*31*	*19*	*9*	*39*	*35*	*36*

Extra Entry Criteria — *Beyond TULIP-2 Entry Criteria:* *Steroid ≤ 40 mg/day & SLEDAI_2K ≥ 6*	***anifrolumab-IV 300mg Q4W** - week 52 **absolutes** - (% achieving response)*						
	Subgroup: Baseline CLASI ≥ 10				*No additional subgroup*		
	CLASI-20	CLASI-50	CLASI-70	CLASI-90	SLEDAI_2K-4	SRI-4	BICLA
High anti_dsDNA (> 100,300 pg/mL)	99	97	85	57	42	62	62
Low C3 (< 9.0e8 pg/mL)	93	81	69	44	35	41	41
Very Low C4 (< 1.0e8 pg/mL)	**100**	**99**	**94**	**76**	50	80	78
Low C4 (< 1.6e8 pg/mL)	**100**	**99**	86	58	50	**82**	**80**
SLEDAI_2K ≥ 8	99	97	87	57	55	62	62
CLASI ≥ 8	*Same as original entry criteria because of subgroup*				**62**	61	59
Swollen Joint Count (SJC) ≥ 4	85	31	17	0	39	73	72
Original Entry Criteria Only	*91*	*65*	*55*	*36*	*44*	*46*	*46*

Example Model Fit with TULIP-2 Entry Criteria vs. Altered Entry Criteria Simulation (SLEDAI_2K ≥ 8)



Extra Entry Criteria — *Beyond TULIP-2 Entry Criteria:* *Steroid ≤ 40 mg/day & SLEDAI_2K ≥ 6*	***(Therapy - Placebo)** - week 52 **Deltas** - difference of percentages in upper tables*							**Trial Inclusion**		**Scoring Metrics**	
	Subgroup: Baseline CLASI ≥ 10				*No additional subgroup*			Inclusion in TULIP-2 *TULIP-2 is 24% of the full SimPops Cohort*	Percentage of Full SimPops Cohort	Sum of deltas *Σ(anifrolumab response - placebo response) across endpoints*	Sum of deltas excluding *CLASI-X* endpoints
	CLASI-20	CLASI-50	CLASI-70	CLASI-90	SLEDAI_2K-4	SRI-4	BICLA				
High anti_dsDNA (> 100,300 pg/mL)	26	29	40	37	5	8	7	54%	13%	153	20
Low C3 (< 9.0e8 pg/mL)	30	28	37	25	5	10	9	52%	12%	144	24
Very Low C4 (< 1.0e8 pg/mL)	35	38	38	**49**	9	19	17	**7%**	**2%**	205	44
Low C4 (< 1.6e8 pg/mL)	27	30	41	38	**9**	12	11	19%	5%	166	31
SLEDAI_2K ≥ 8	**47**	**50**	**55**	42	4	15	14	**67%**	**16%**	**229**	34
CLASI ≥ 8	*Same as original entry criteria because of subgroup*				8	**37**	**34**	21%	5%	214	**80**
Swollen Joint Count (SJC) ≥ 4	13	3	14	0	6	1	1	17%	4%	37	7
Original Entry Criteria Only	*37*	*34*	*36*	*27*	*5*	*11*	*10*	*100%*	*24%*	*161*	*27*

Green highlighting indicates favorable results relative to the original entry criteria.

Bold green indicates the best result within each set.

Red indicates the lowest trial inclusion.

CONCLUSION

- Enrichment can increase absolute response without improving separation between therapy and placebo, and reduces inclusion opportunity.
  - Our QSP framework quantifies that trade-off prospectively.
- This framework supports trial design decision-making.
  - It has been applied prospectively for novel-compound predictions in prior pharmaceutical development partnerships.
- This analysis supports patient-level precision medicine decisions.
  - Using commonly tested biomarkers and clinical outputs, clinicians can use the results of this analysis to estimate patient-specific probabilities of clinically relevant responses for a given treatment, exemplified here by 300 mg IV Q4W anifrolumab.

REFERENCES

- 1) Simulations Plus, Inc.
- 2) Furie R, et al. Anifrolumab in Systemic Lupus Erythematosus (MUSE). Arthritis Rheumatol. 2017;69(2):376-386. PMID: 27992695.
- 3) Morand EF, et al. Trial of Anifrolumab in Active Systemic Lupus Erythematosus (TULIP-2). N Engl J Med. 2020;382(3):211-221. PMID: 31851731.
- *Full list of references available upon request.*

ACKNOWLEDGEMENTS

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Thales

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