Safety and efficacy of CABA-201, a fully human, autologous 4-1BB anti-CD19 CAR T cell therapy in patients with immune-mediated necrotizing myopathy and systemic lupus erythematosus from the RESET-Myositis™ and RESET-SLE™ clinical trials

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Disclosures

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Tahseen Mozaffar		**Advisor or Review Panel Member, Grant/Research Support:** Amicus; AnnJi; Argenx; Astellas Gene Therapy; AstraZeneca; Janssen; Sanofi; Spark Therapeutics; UCB **Advisor or Review Panel Member:** Arvinas; AskBio; Horizon Therapeutics; Maze Therapeutics; Sarepta **Grant/Research Support:** Bristol-Myers Squibb (BMS); Cartesian Therapeutics; Grifols; ML-Bio; Valerion
Vimal Derebail		**Consultant:** Amgen; Forma Therapeutics (NovoNordisk); iCell Gene; Novartis
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Autoimmune Disease Patients Face Substantial Unmet Medical Needs

Despite therapies with chronic broad immunosuppression, mortality is increased, and quality of life is reduced*[1–4]

Myositis

- Chronic inflammation often leads to permanent tissue damage[1]
- Progressive weakness, pain, dysphagia, and extramuscular manifestations are also common[5]

Systemic lupus erythematosus

- Progressive, multi-organ damage[6]
- ~40% develop lupus nephritis with 25% risk of death or ESKD within 10 years[7,8]

Systemic sclerosis

- Progressive skin and organ fibrosis, which often leads to irreversible lung, cardiac and kidney damage[2]
- Average survival from diagnosis is ~12 years[9]

Patients are seeking a drug-free, symptom-free life; physicians also prioritize prevention of end-organ damage[10]

*Compared with the general population; ESKD, end-stage kidney disease.

1. Lundberg IE, et al. *Nat Rev Dis Primers*. 2021;7(1):86. 2. Allanore Y, et al. *Nat Rev Dis Primers*. 2015;1:15002. 3. Zen M, et al. *Eur J Intern Med*. 2023;112:45–51. 4. Refai RH, et al. *Sci Rep*. 2024;14(1):5234. 5. Suh J, Amato AA. *Muscle Nerve*. 2024;70(2):166–172. 6. Murimi-Worstell IB, et al. *BMJ Open*. 2020;10(5):e031850. 7. Anders HJ, et al. *Nat Rev Dis Primers*. 2020;6(1):7. 8. Hoover PJ, Costenbader KH. *Kidney Int*. 2016;90(3):487–492. 9. Mayes MD. *Rheum Dis Clin North Am*. 2003;29(2):239–254. 10. Golder V, et al. *Lupus*. 2018;27(3): 501–506.

What are Chimeric Antigen Receptor (CAR) T Cells?

Engineered T cells that combine the targeting ability of antibodies with the cell-killing machinery of T cells[1]

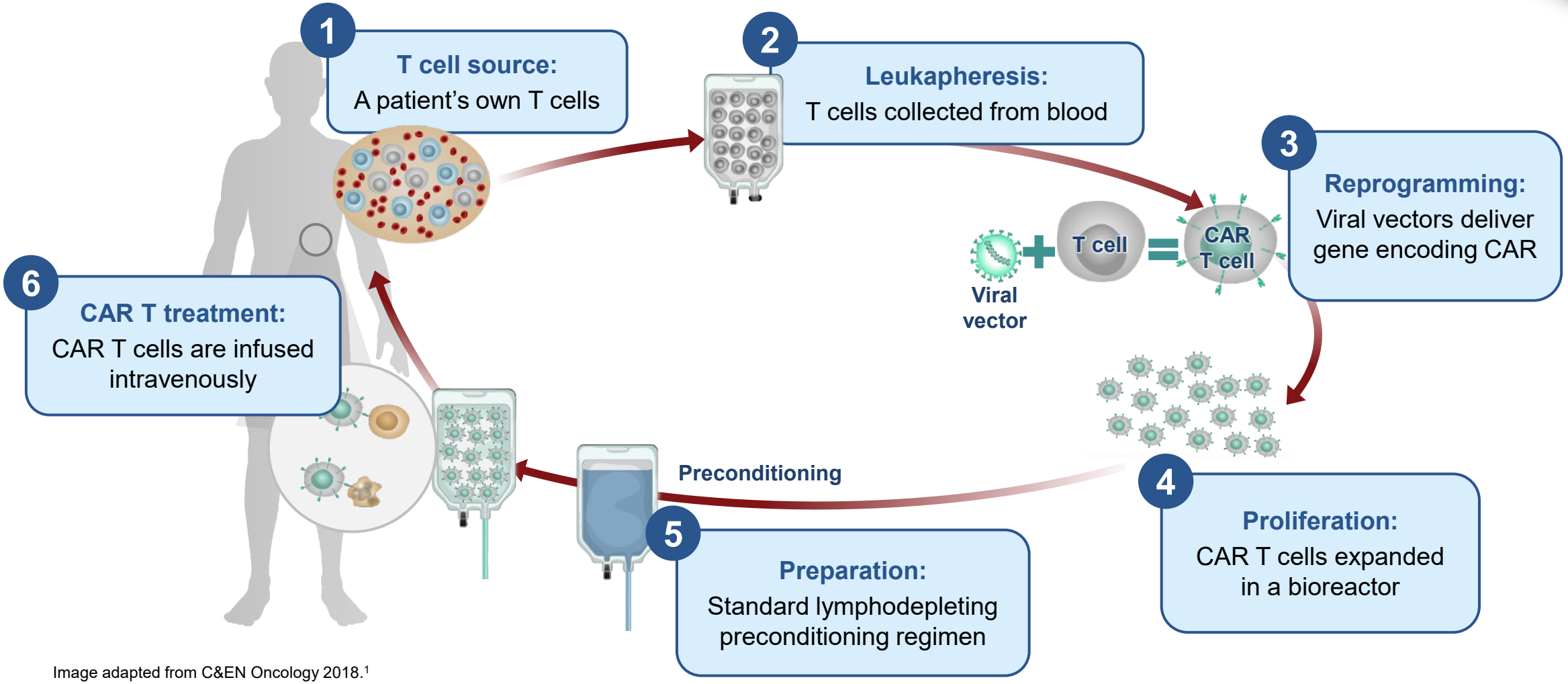


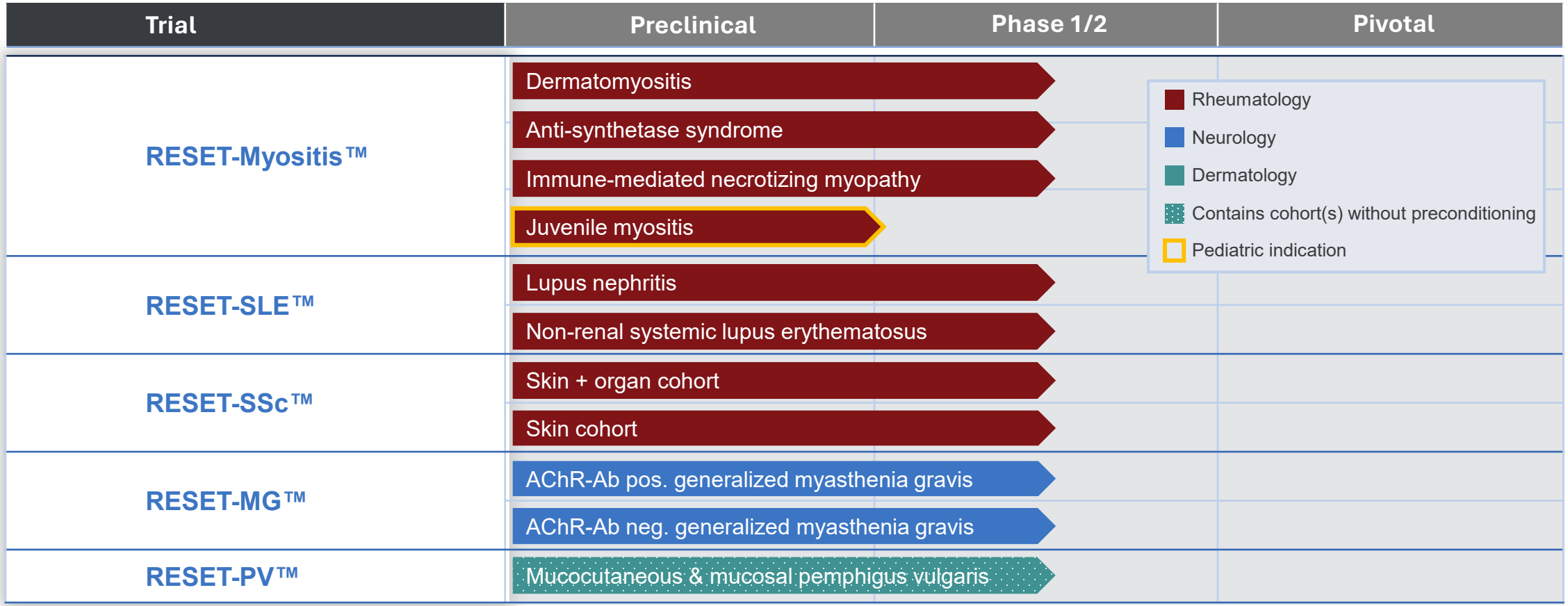
Image adapted from C&EN Oncology 2018.[1]

CAR, chimeric antigen receptor.

1. C&EN Oncology. 2024. Available at: https://cen.acs.org/pharmaceuticals/oncology/Controlling-CAR-T-scientists-plan/96/i19 (accessed October 2024).

RESET™ Clinical Program for CABA-201, a CD19-directed CAR T

Multiple autoimmune diseases evaluated in distinct disease cohorts enrolling at 40 US sites



AChR-Ab, acetylcholine receptor antibody; CABA, Cabaletta Approach to B cell Ablation; CAR, chimeric antigen receptor; RESET, REstoring SElf-Tolerance.
Cabaletta Bio: CABA-201. Available at: www.cabalettabio.com/pipeline/caba-201 (accessed October 2024).

RESET™ Program: Key Inclusion and Exclusion Criteria

Designed to evaluate the safety and tolerability of CABA-201 in subjects with active, refractory disease

Key inclusion criteria[1–3]

Evidence of active disease despite prior or current treatment with standard of care

RESET-Myositis™

- Age ≥18 and ≤75 with a diagnosis of IIM (ASyS, DM, or IMNM)
- Presence of at least one MSA
- **JIIM**: Age ≥6 and ≤17 with presence of at least one MSA or MAA

RESET-SLE™

- Age ≥18 and ≤65 with an SLE diagnosis
- Positive ANA or anti-dsDNA at screening
- **SLE (non-renal)**: active, moderate to severe SLE, SLEDAI-2K ≥8; pure class V LN patients eligible for this cohort
- **LN**: active, biopsy-proven LN class III or IV (± class V)

RESET-SSc™

- Age ≥18 and ≤70 with a limited or diffuse SSc diagnosis
- Evidence of significant skin, pulmonary, renal, or cardiac involvement

Key exclusion criteria[1–3]

B cell-depleting agent within prior 3-6 months; Previous CAR T therapy and/or HSCT

- Cancer-associated myositis
- Significant lung or cardiac impairment

- Presence of kidney disease other than LN
- Current symptoms of severe, progressive, or uncontrolled pulmonary or cardiac disease

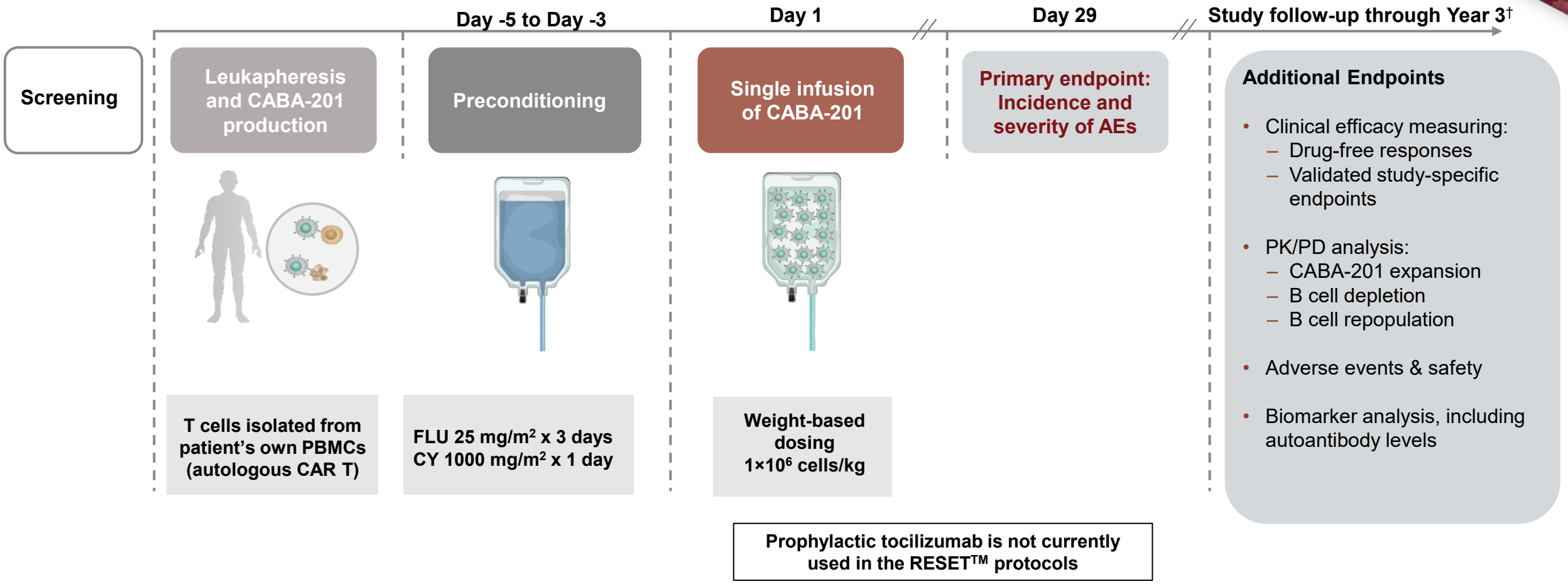
- Severe lung or cardiac impairment

ANA, antinuclear antibody; anti-dsDNA, anti-double strand DNA antibodies; ASyS, antisynthetase syndrome; CAR, chimeric antigen receptor; DM, dermatomyositis; HSCT, hematopoietic stem cell transplantation; IIM, idiopathic inflammatory myopathy; IMNM, immune mediated necrotising myopathy; JIIM, juvenile idiopathic inflammatory myopathy; LN, lupus nephritis; MAA, myositis-associated antibody; MSA, myositis-specific antibodies; SLEDAI-2k, SLE disease activity index 2000; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

1. ClinicalTrials.gov. Available at: www.clinicaltrials.gov/study/NCT06121297 (accessed October 2024). 2. ClinicalTrials.gov. Available at: www.clinicaltrials.gov/study/NCT06328777 (accessed October 2024). 3. ClinicalTrials.gov. Available at: www.clinicaltrials.gov/study/NCT06154252 (accessed October 2024).

RESET™ Clinical Trials Have Consistent Design Principles[1]

Individual trials in myositis, SLE, and SSc share common elements of preconditioning, dose, and study design



†Follow up period encompasses 15 years in total, aligned to regulatory guidance for CAR T cell therapies.

AE, adverse event; CABA, Cabaletta Approach to B cell Ablation; FLU, fludarabine; CY, cyclophosphamide; PBMC, peripheral blood mononuclear cell; PD, pharmacodynamics; PK, pharmacokinetics; RESET, REstoring SElf-Tolerance; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

Cabaletta Bio: Data on file; 1. Peng BJ, et al. *Mol Ther Methods Clin Dev*. 2024;32(2):101267.

Baseline Characteristics: First 8 Patients in the RESET™ Program

All patients had active, refractory disease and most had failed B cell-targeting therapies

	RESET-Myositis™			RESET-SLE™				RESET-SSc™
Patient / Cohort	**IMNM-1**	**IMNM-2**	**DM-1**	**SLE-1**† Class V LN	**SLE-2**	**SLE-3**	**LN-1**	**SSc-Skin-1** (severe skin cohort)
Age, sex	33 M	60 M	57 M	26 M	36 F	44 F	24 F	66 F
Disease duration	~2 years	~4 years	~4 years	~6 years	~17 years	~9 years	~2 years	~2 years
Autoantibodies	SRP	HMGCR	SAE	dsDNA	dsDNA	dsDNA	dsDNA	RNA P III
Baseline Disease activity*	**MMT-8**			**SLEDAI-2K**				**mRSS**
	130	126	131	26	10	8	22	42
	CK (U/L)			**UPCR (mg/mg)**				
	617	4725	94	1.08†	n/a	n/a	7.22	
Therapies at Screening	GC, MTX	GC, IVIG	GC, MMF, HCQ	GC, MMF, HCQ	GC, AZA, HCQ	HCQ, MMF, BEL	GC, ANI, VOC, MMF, HCQ	MMF
Other prior therapies	RTX, IVIG	RTX, MMF, MTX	IVIG	CYC, BEL, VOC, TAC	MSC, RTX, ANI, BEL, ADA, MTX	GC, MTX	BEL, LEF	HCQ
GC dose at Screening (mg/day)	5	5	20	10	7	n/a	20	n/a

*Baseline disease activity = activity before preconditioning.
†SLE-1 had class V LN; inclusion criteria for LN cohort requires class III/IV LN.
ADA, adalimumab; ANI, anifrolumab; AZA, azathioprine; BEL, belimumab; CK, creatinine kinase; CYC, cyclophosphamide; DM, dermatomyositis; dsDNA, double-stranded DNA; GC, glucocorticoid; HCQ, hydroxychloroquine; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; IMNM, immune-mediated necrotizing myopathy; IVIG, intravenous immunoglobulin; LEF, leflunomide; LN, lupus nephritis; MMF, mycophenolate mofetil; MMT-8, manual muscle testing 8; mRSS, modified Rodnan skin score; MSC, mesenchymal stem cell; MTX, methotrexate; RESET, REstoring SElf-Tolerance; RNA P III, RNA polymerase III; RTX, rituximab; SAE, small ubiquitin-like modifier activating enzyme; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE disease activity index 2000; SRP, signal recognition particle; SSc, systemic sclerosis; TAC, tacrolimus; U/L, units per liter; UPCR, urinary protein-to-creatinine ratio; VOC, voclosporin.
Cabaletta Bio: Data on file.

Incidence and Severity of Adverse Events*

	RESET-Myositis™			RESET-SLE™				RESET-SSc™
Cohort	**IMNM**		**DM**	**Non-renal SLE**			**LN**	**SSc – Severe Skin**
Patient	**IMNM-1**	**IMNM-2**	**DM-1**	**SLE-1**	**SLE-2**	**SLE-3**	**LN-1**	**SSc-Skin-1**
CRS†	None	None	None	None	Grade 1	None	Grade 1	Grade 2
ICANS†	None	None	None	None	None	None	Grade 4	None
Serious infections‡	None	None	None	None	None	None	None	None
Hypogammaglobulinemia	None	None	None	None	None	None	Grade 2	None
Related SAEs (Grade)§ (excluding CRS and ICANS)	None	None	None	None	None	None	Fever (1) Pancytopenia¶ (4)	None
Unrelated SAEs (Grade)§	None	Back Pain (3) PE# (4)	None	None	None	None	None	Neutropenia (4) (FLU/CY related)

*As of Nov 1, 2024; Primary endpoint is incidence and severity of Adverse Events through Day 29. †Graded per ASTCT Consensus Grading Criteria. Of these patients, only DM-1, SLE-2, SLE-3, and SSc-Skin-1 **received** medication for seizure prophylaxis. Tocilizumab was **not** administered for any cases of CRS. ‡Coded in System Organ Class of Infections and Infestations and meets seriousness criteria. §As assessed per FDA guidelines.

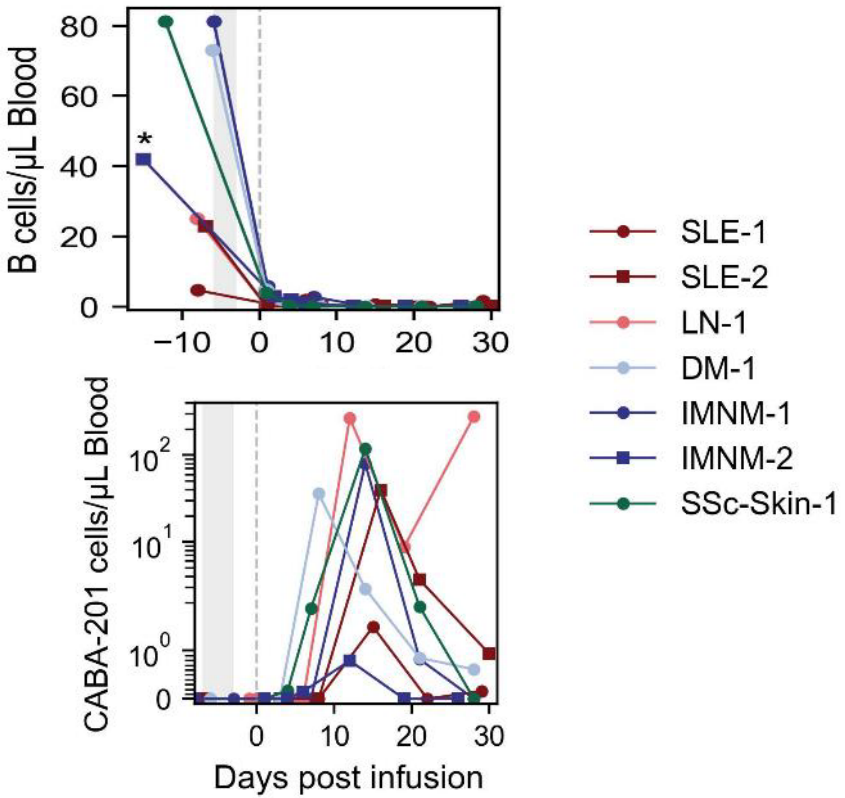
#Patient with Factor V Leiden heterozygosity (increased risk for thrombosis), recent intravenous immunoglobulin treatment, history of myocardial infarction, recent hospitalization for back pain & fatigue with decreased mobility. Undetectable CABA-201 levels since Day 22. Event occurred at Day 38 and was reported as PE leading to cardiac arrest, followed by successful pulmonary artery thrombectomy.
¶Consistent with "Prolonged Cytopenias," which is a labeled warning and precaution for approved oncology CAR T products.

CRS, cytokine release syndrome; CY, cyclophosphamide; DM, dermatomyositis; FLU, fludarabine; ICANS, immune effector cell-associated neurotoxicity syndrome; IMNM, immune-mediated necrotizing myopathy; LN, lupus nephritis; PE, pulmonary embolism; SAE, serious adverse event; RESET, REstoring SElf-Tolerance; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.
Cabaletta Bio: Data on file.

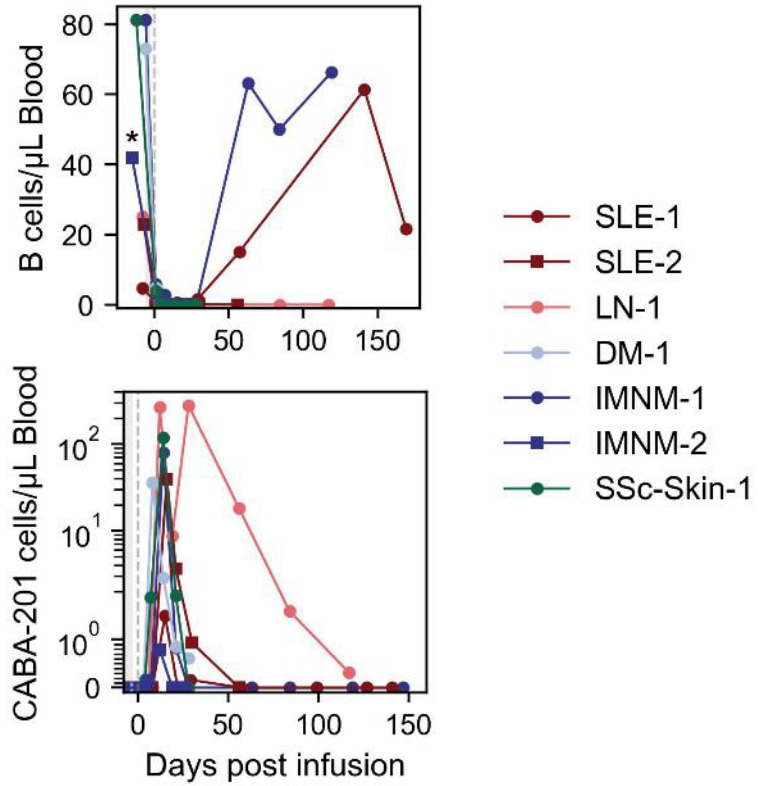
Consistent and Complete B cell Depletion by Day 22[1]

In patients with >3-month follow-up, B cell repopulation with naïve cells started as early as 8 weeks

B cell depletion & CABA-201 expansion through Day 30



B cell depletion/repopulation & CABA-201 expansion through Day 150



CABA-201 exhibited a PK/PD profile with peak expansion between Day 8 and 15 as expected, with a later 2nd peak for LN-1

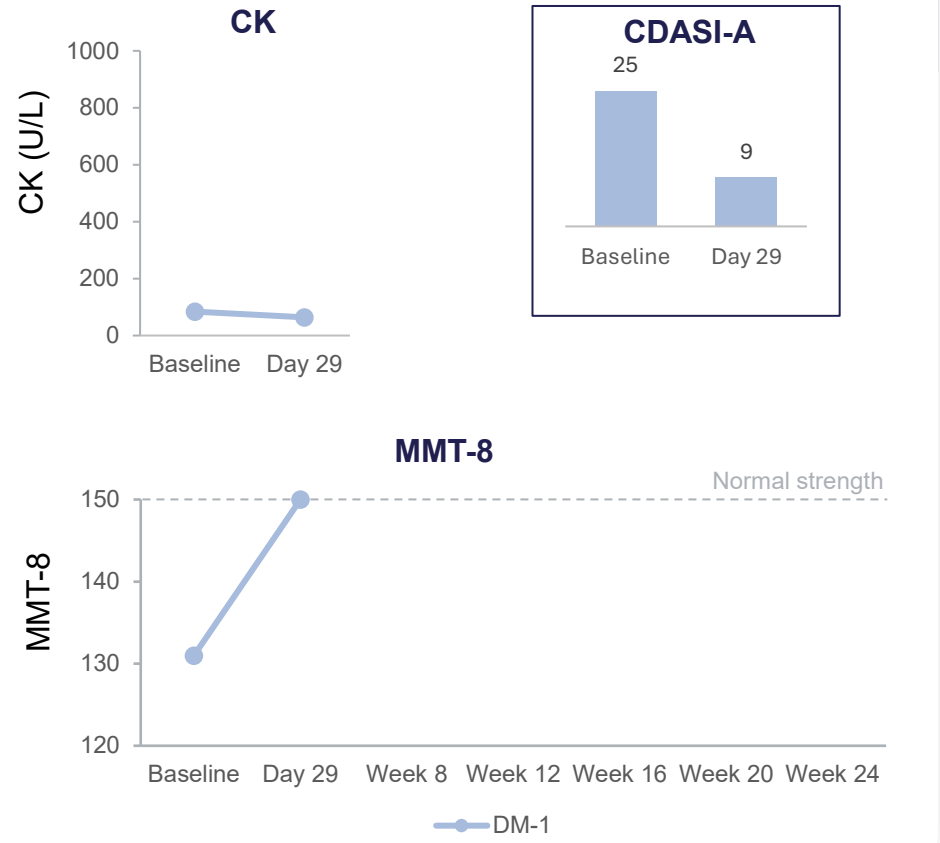
PK, pharmacokinetic; PD, pharmacodynamic.

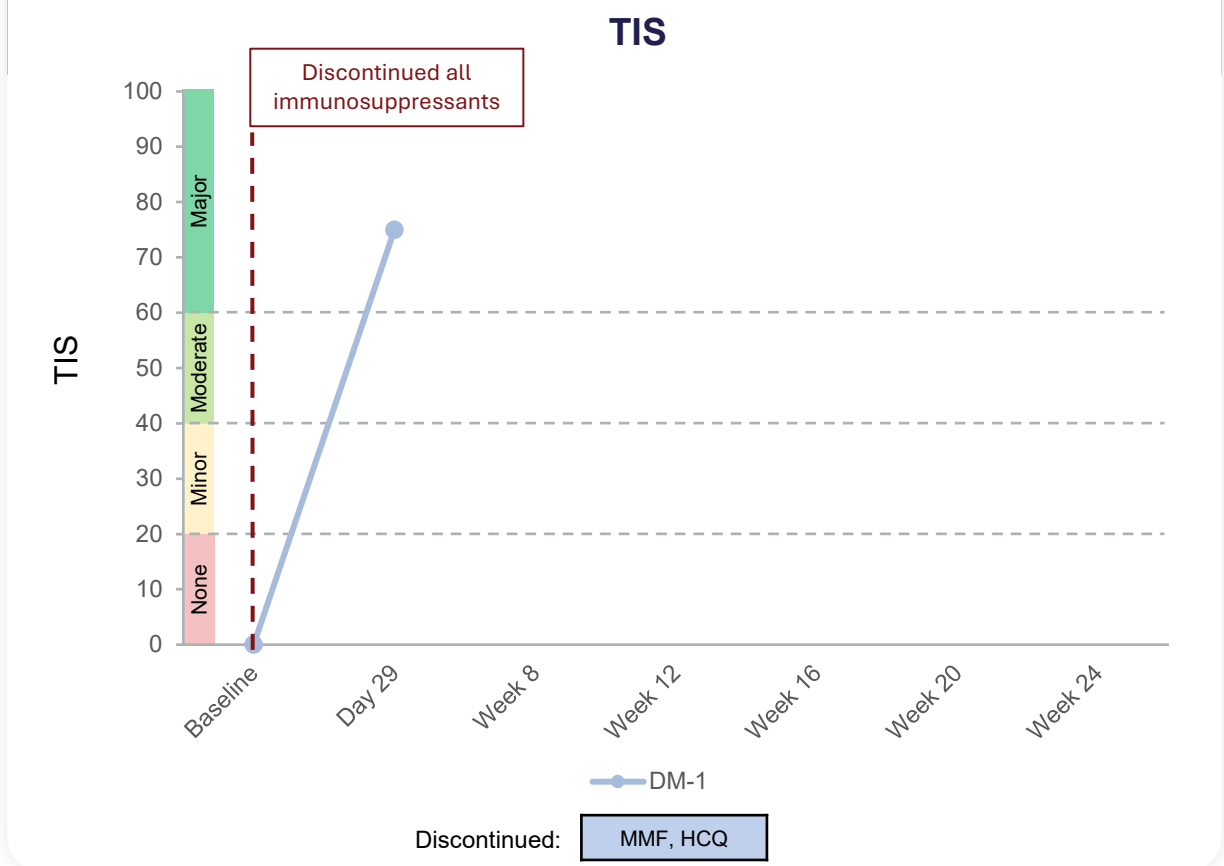
*Pre-infusion B-cell levels were measured at pre-preconditioning for all subjects other than IMNM-2 where apheresis was used.

1. Nunez et al. Correlative Studies of CABA-201 from the RESET-Myositis™ and RESET-SLE™ Clinical Trials. Presented at ACR Convergence 2024. Abstract 0324.

RESET- Myositis™: Early Efficacy Data Following CABA-201 Infusion

1st known adult DM patient dosed with CAR T demonstrated compelling early clinical response off immunosuppressants‡





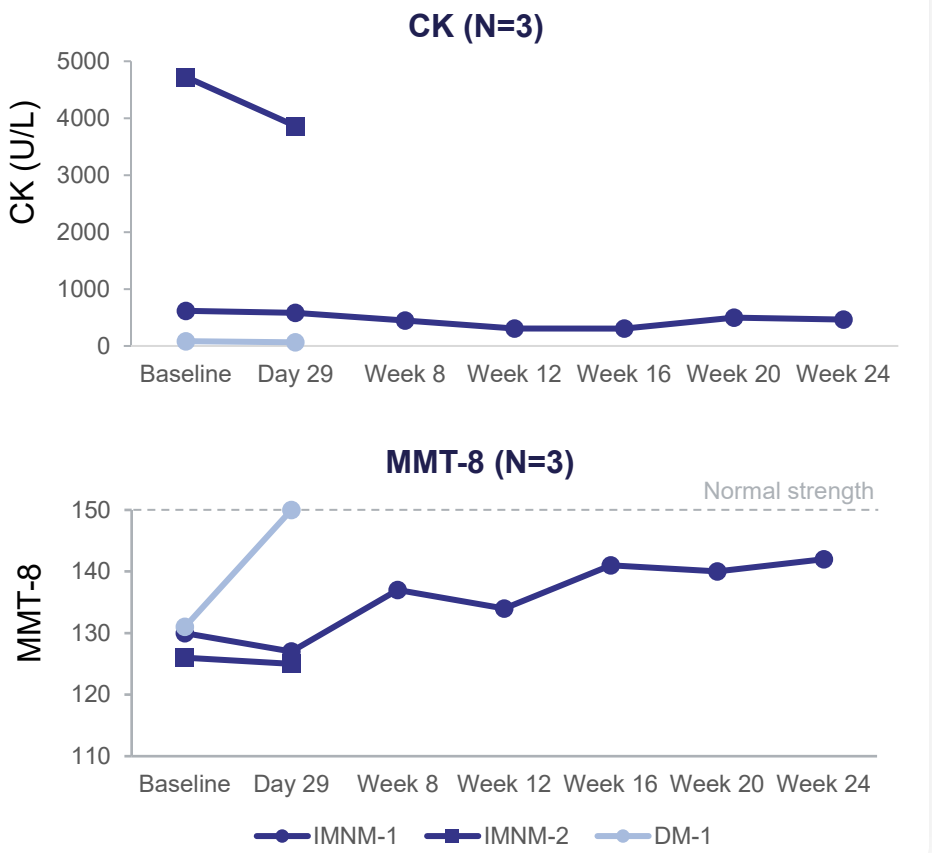
‡As of Nov 1, 2024.

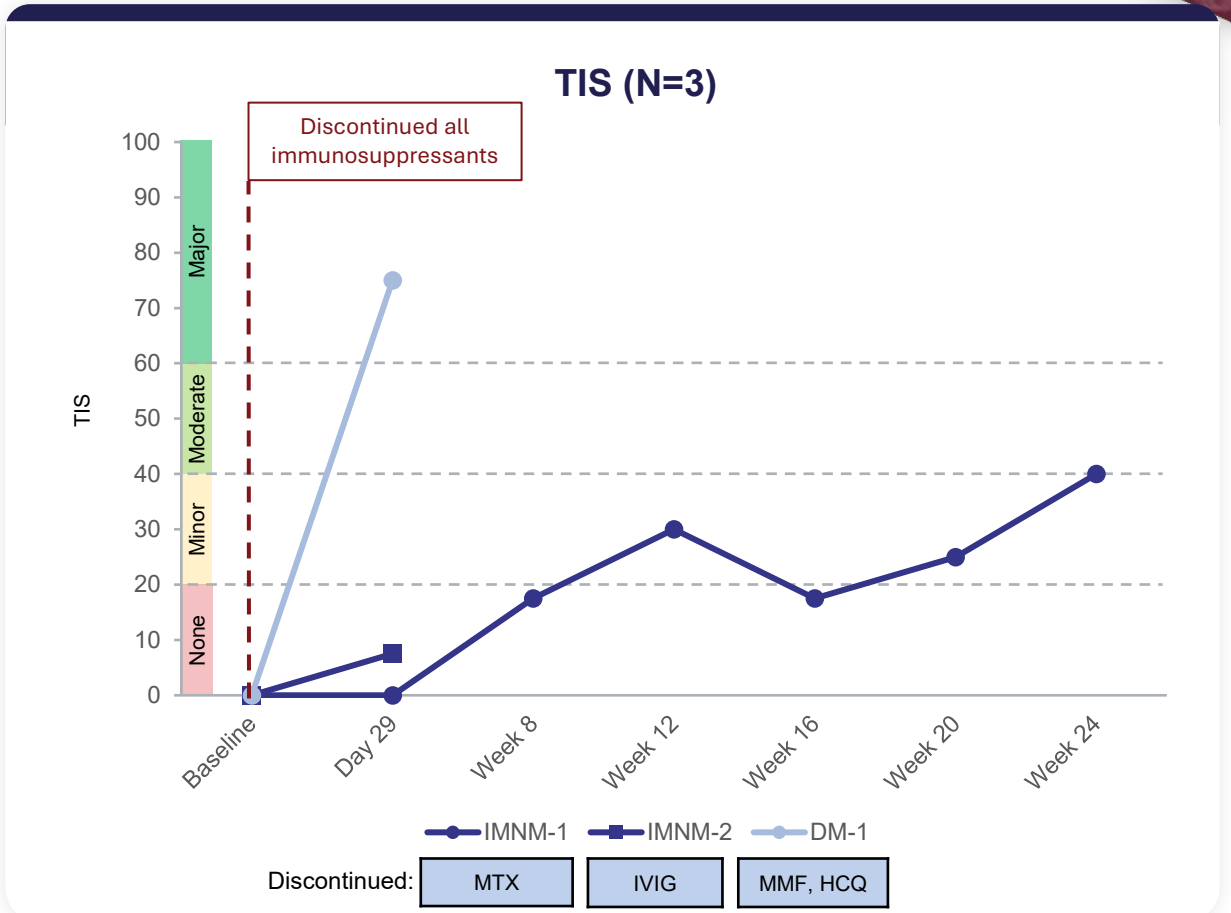
CAR, chimeric antigen receptor; CDASI-A, Cutaneous Dermatomyositis Disease Area and Severity Index – Activity; CK, creatinine kinase; DM, dermatomyositis; GC, glucocorticoid; HCQ, hydroxychloroquine; IMNM, immune-mediated necrotizing myopathy; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil; MMT-8, manual muscle testing 8; RESET, REstoring SElf-Tolerance; TIS, total improvement score; U/L, units per liter.

Cabaletta Bio: Data on file.

RESET-Myositis™: Efficacy Data Following CABA-201 Infusion

1st IMNM patient with longer follow up demonstrated continuing clinical response off immunosuppressants without flares‡





Initial clinical responses in IMNM are consistent with published data[1]; response kinetics may differ among myositis subtypes

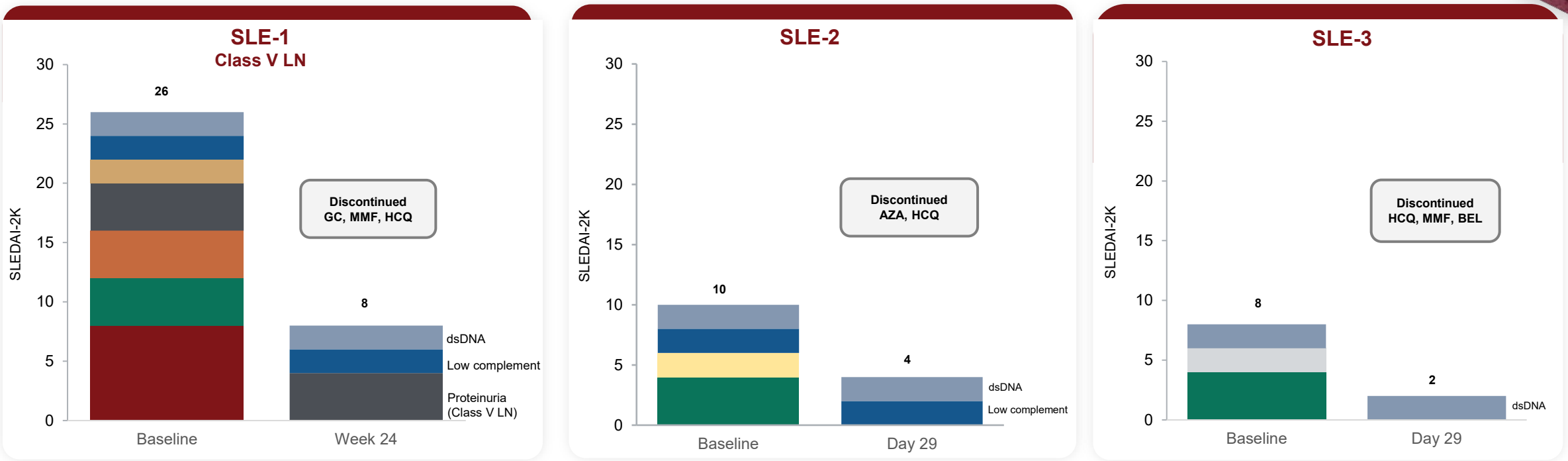
‡As of Nov 1, 2024.

CDASI-A, Cutaneous Dermatomyositis Disease Area and Severity Index – Activity; CK, creatinine kinase; DM, dermatomyositis; GC, glucocorticoid; HCQ, hydroxychloroquine; IMNM, immune-mediated necrotizing myopathy; IVIG, intravenous immunoglobulin; MTX, Methotrexate; MMF, mycophenolate mofetil; MMT-8, manual muscle testing 8; RESET, REstoring SElf-Tolerance; TIS, total improvement score; U/L, units per liter.

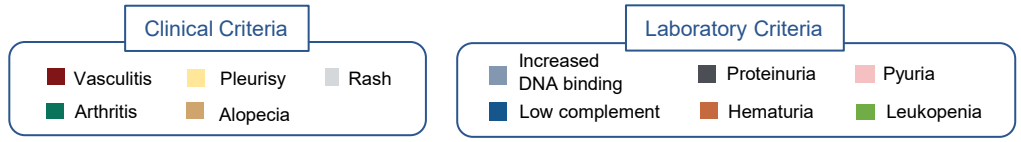
Cabaletta Bio: Data on file. 1. Schett, G. 'CAR-T Cell Therapy: "The Future is Now."' 5th Global Conference on Myositis. iMyoS. Pittsburgh, PA.

RESET-SLE™: Efficacy Data in SLE Following CABA-201 Infusion

All 3 SLE patients demonstrated clinical responses off immunosuppressants; longer follow-up patient SLE-1 completed steroid taper‡



No clinical symptoms on SLEDAI-2K through latest follow up, including SLE-1 with isolated Class V LN (non-renal cohort) with persistent proteinuria as expected



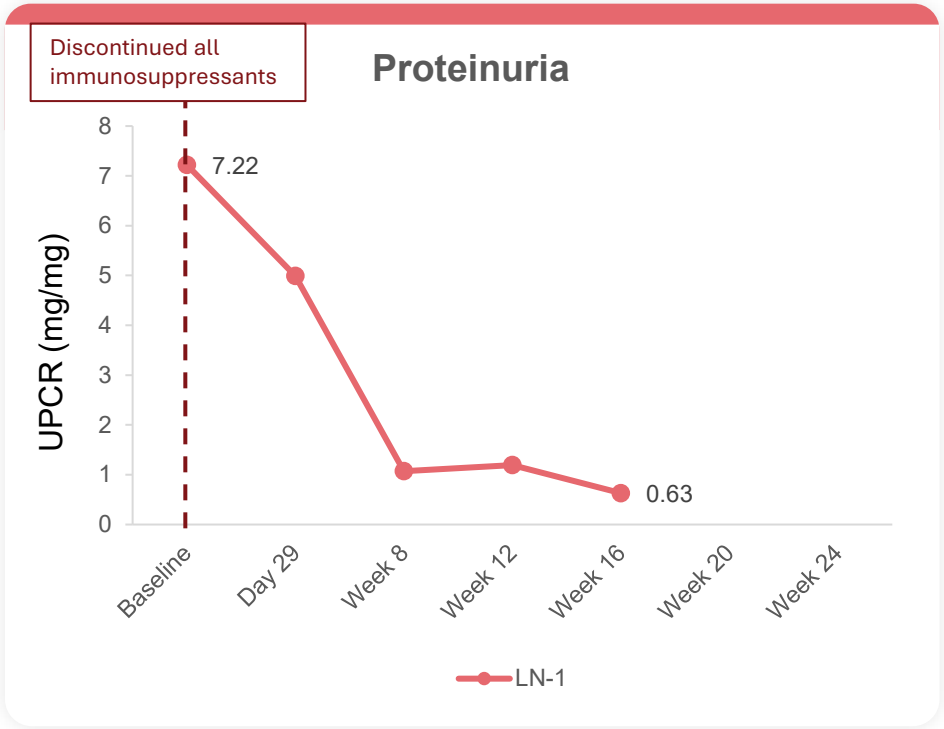
‡As of Nov 1, 2024

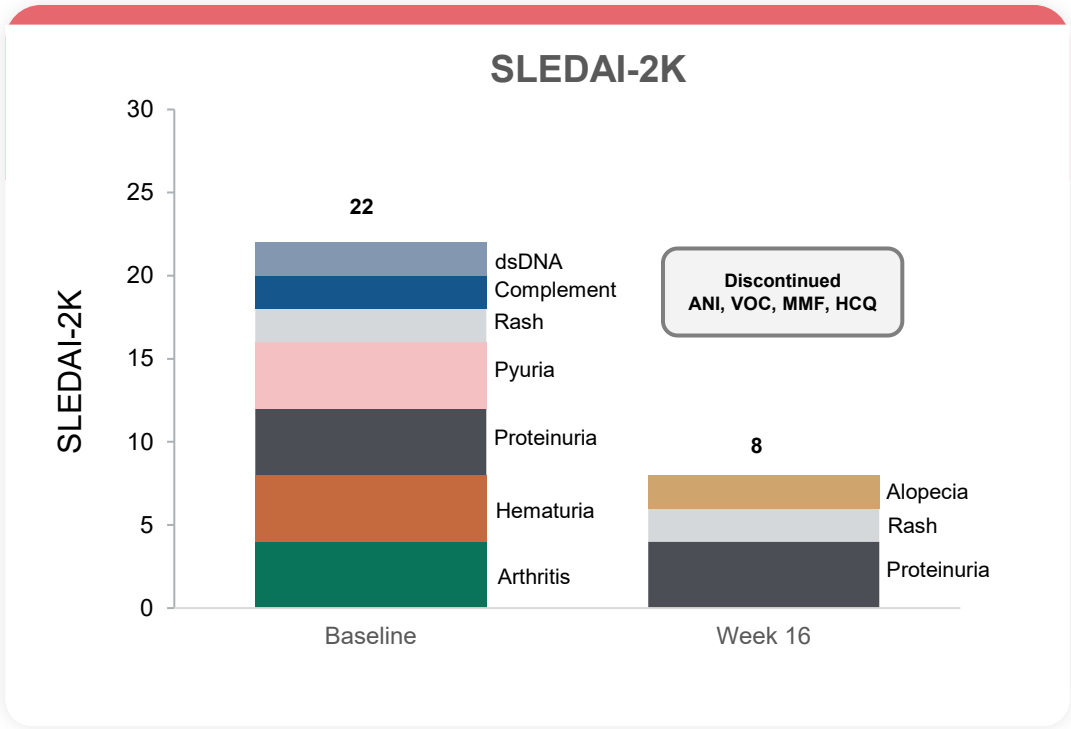
AZA, azathioprine; BEL, belimumab; GC, glucocorticoid; dsDNA, double-stranded DNA; HCQ, hydroxychloroquine; LN, lupus nephritis; MMF, mycophenolate mofetil; RESET, REstoring SElf-Tolerance; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

Cabaletta Bio: Data on file.

RESET-SLE™: Efficacy Data in LN Following CABA-201 infusion

LN-1 demonstrated marked improvement of proteinuria off all immunosuppressants, continuing steroid taper ‡





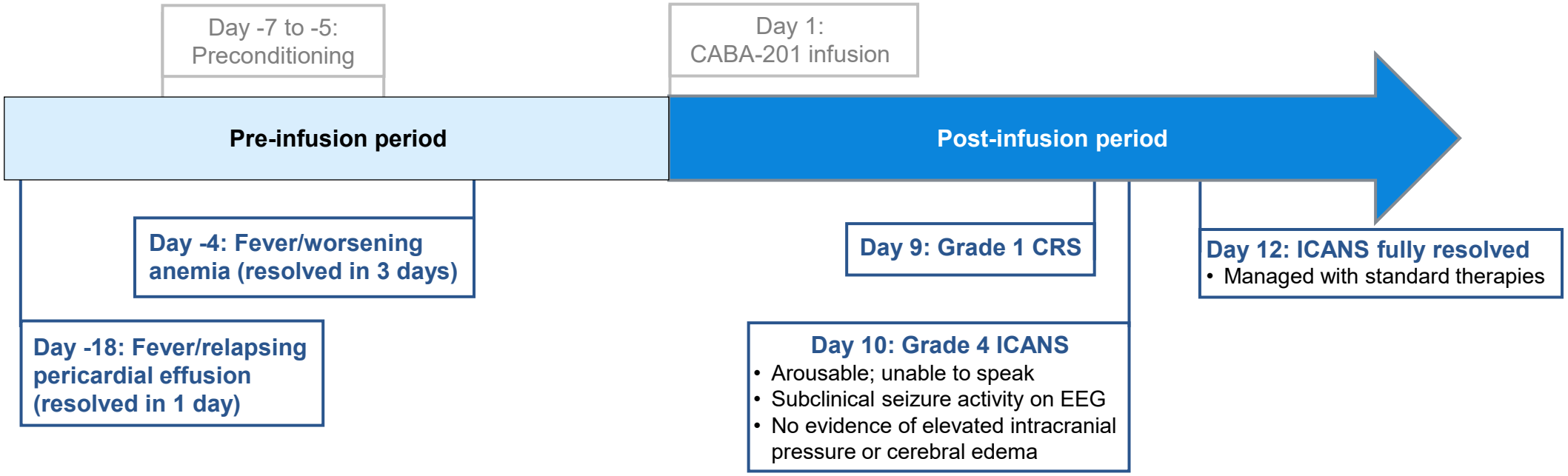
LN-1 proteinuria markedly improved by Week 8 with alopecia/rash as the remaining clinical manifestations at Week 16 after discontinuation of all immunosuppressants and continuing prednisone taper

‡As of Nov 1, 2024.
ANI, anifrolumab; dsDNA, double-stranded DNA; HCQ, hydroxychloroquine; LN, lupus nephritis; MMF, mycophenolate mofetil; RESET, REstoring SElf-Tolerance; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; UPCR, urinary protein-to-creatinine ratio; VOC, voclosporin.
Cabaletta Bio: Data on file.

LN-1 Patient : ICANS Event Timeline

Patient with recent fever in setting of acute and severe inflammation

- 24-year-old female with SLE for ~2 years and with active class III LN
- Active, severe (SLEDAI-2K = 22; UPCR = 7.22 mg/mg) refractory disease despite 5 systemic treatments* for SLE at screening



Patient had acute, febrile inflammatory events and highly elevated pro-inflammatory cytokines (MIP-1β, IL-27) prior to infusion that continued after treatment, suggesting a possible occult infection; supportive data from TCR clonal sequencing[1]

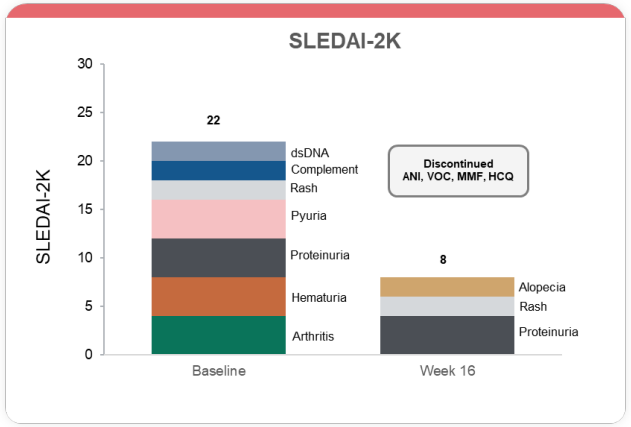
*Therapies at Screening: glucocorticoids, anifrolumab, voclosporin, mycophenolate mofetil, hydroxychloroquine.
CRS, cytokine release syndrome; EEG, electroencephalogram; ICANS, immune effector cell-associated neurotoxicity syndrome; LN, lupus nephritis; RESET, REstoring SElf-Tolerance; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; TCR, T Cell Receptor; UPCR, urinary protein-to-creatinine ratio.
Cabaletta Bio: Data on file. 1. Nunez et al. Correlative Studies of CABA-201 from the RESET-Myositis™ and RESET-SLE™ Clinical Trials. Presented at ACR Convergence 2024. Abstract 0324.

LN-1 Patient Outcome: 4 Months Post-Treatment

Compelling clinical response since discontinuation of all immunosuppressants, continuing steroid taper

Patient 4 Months Follow-up*

- Off all immunosuppressants‡
- Prednisone 8mg/day; taper ongoing
- SLEDAI-2K: 22 → 8
- UPCR (mg/mg): 7.22 → 0.63



"Overall, I feel much better than I felt before CABA-201 therapy. I have much more energy, I have significantly less joint pain and inflammation, my proteinuria has improved, I no longer have any mouth sores, and I am getting back to my normal self!

At 25 years old, my kidneys were not functioning properly and continued to get worse despite all of the strong medications I was on. I had multiple occurrences of fluid around my heart. CABA-201 has put a stop to that and has allowed my body to heal. Although I faced complications afterwards, I believe the improvement that I have seen in both my numbers and how I feel, was far worth it.

If I had the choice, I would choose to receive CABA-201 again…. "

- LN-1 patient at 4 months post-therapy

*As of Nov 1, 2024.

‡Therapies at Screening: glucocorticoids, anifrolumab, voclosporin, mycophenolate mofetil, hydroxychloroquine.

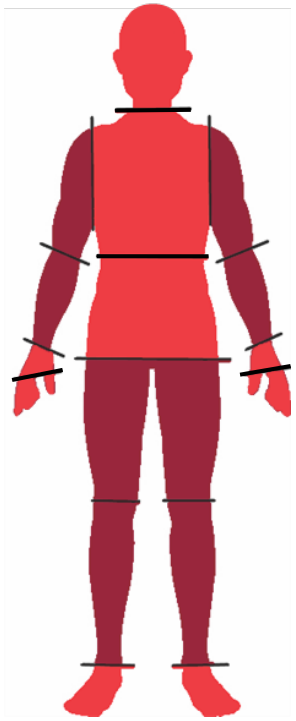
ANI, anifrolumab; dsDNA, double-stranded DNA; HCQ, hydroxychloroquine; LN, lupus nephritis; MMF, mycophenolate mofetil; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; UPCR, urinary protein-to-creatinine ratio; VOC, voclosporin.

Cabaletta Bio: Data on file.

RESET-SSc™: Emerging Efficacy Data - 42 days post infusion

Early disease improvements in face and hands after discontinuation of disease-specific medication

Baseline mRSS score by body area
SSc-Skin-1



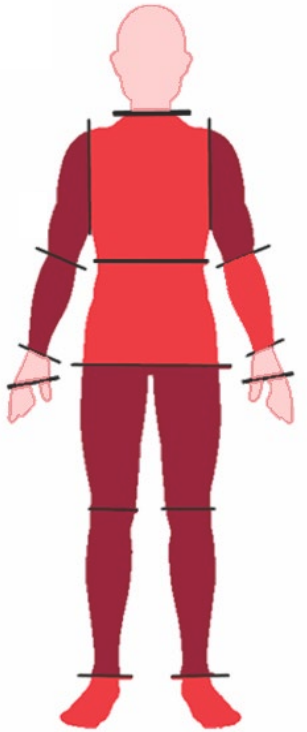
- 0 None
- 1 Mild
- 2 Moderate
- 3 Severe

Overall mRSS score
SSc-Skin-1

	Baseline	Day 22	Day 42
mRSS	42	38	36

- Modified Rodnan Skin Score (mRSS): a measure of skin thickness in SSc across 17 body areas, with a maximum score of 51[1]
- Used as an outcome measure in SSc clinical trials as a surrogate for disease activity, severity and mortality[1]

Day 42 mRSS score by body area
SSc-Skin-1



- 0 None
- 1 Mild
- 2 Moderate
- 3 Severe

Early clinical data indicate potential emergence of a drug-free clinical response‡

‡As of Nov 1, 2024 patient is not taking immunosuppressants or steroids.
mRSS, modified Rodnan Skin Score; RESET, REstoring SElf-Tolerance; SSc, systemic sclerosis.
Cabaletta Bio: Data on file. 1. Khanna D, et al. *J Scleroderma Relat Disord*. 2017;2(1):11–18.

Summary from Clinical and Translational Data on the First 8 Patients

- CABA-201 appears to have a favorable risk-benefit profile
  - In patients with recent fever or infections, delaying CAR T infusion should be considered
- CABA-201 provided compelling efficacy in highly active and refractory autoimmune patients through the follow-up period
- Initial data support the potential for drug-free clinical responses
  - All patients discontinued all immunosuppressants
  - SLE patients with longer follow-up: steroid taper completed or ongoing (prednisone 8mg/day)
- The PK/PD data support the current dose of CABA-201[1]

CAR, chimeric antigen receptor; PK, pharmacokinetic; PD, pharmacodynamic; SLE, systemic lupus erythematosus

1. Nunez et al. Correlative Studies of CABA-201 from the RESET-Myositis™ and RESET-SLE™ Clinical Trials. Presented at ACR Convergence 2024. Abstract 0324

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Cabaletta Bio team

- Biostatistics
- Clinical Development
- Clinical Operations
- Computational Biology
- Manufacturing
- Medical Affairs
- Translational Medicine