A Phase II Controlled Trial of Human Allogeneic Umbilical Cord-Derived Mesenchymal Stem Cells (MSCs) for the Treatment of Refractory Lupus

A double-blind placebo-controlled safety & efficacy trial

Principal Investigator: Gary S. Gilkeson, MD
Protocol Chair: Diane L. Kamen, MD, MSCR

Trial Management: MUSC Data Coordination Unit (DCU)

MUSC Health
Medical University of South Carolina
Changing What's Possible

The So Very Fine Nine

- **Active Sites**
- **Cedars – Sinai**
  - Mariko Ishimori, MD – PI; Bonnie Paul – Coordinator
- **Emory University School of Medicine**
  - Sam Lim, MD, MPH – PI; Karla Caylor – Coordinator
- **Northwestern University**
  - Rosalind Ramsey-Goldman, MD – PI; Holly Milaeger – Coordinator
- **Medical University of South Carolina**
  - Gary S. Gilkeson, MD – PI; Diane Kamen, MD – co-I; Angela Brown – Coordinator
- **University of California - San Diego**
  - Kenneth Kalunian, MD – PI; Erica Brodie – Coordinator
- **University of North Carolina – Chapel Hill**
  - Saira Z. Sheikh, MD – PI; Sandy Grubbs – Coordinator
- **University of Rochester**
  - Ummara Shah, MD – PI; Maria Allen – Coordinator
- **New Sites**
- **Feinstein Institutes for Medical Research, Manhasset, NY**
  - Meggan Mackey, MD – PI; Andrew Shaw – Coordinator
- **Oklahoma Medical Research Foundation (OMRF), Oklahoma City, OK**
  - Cristina Arriens, MD – PI; TBA – Coordinator

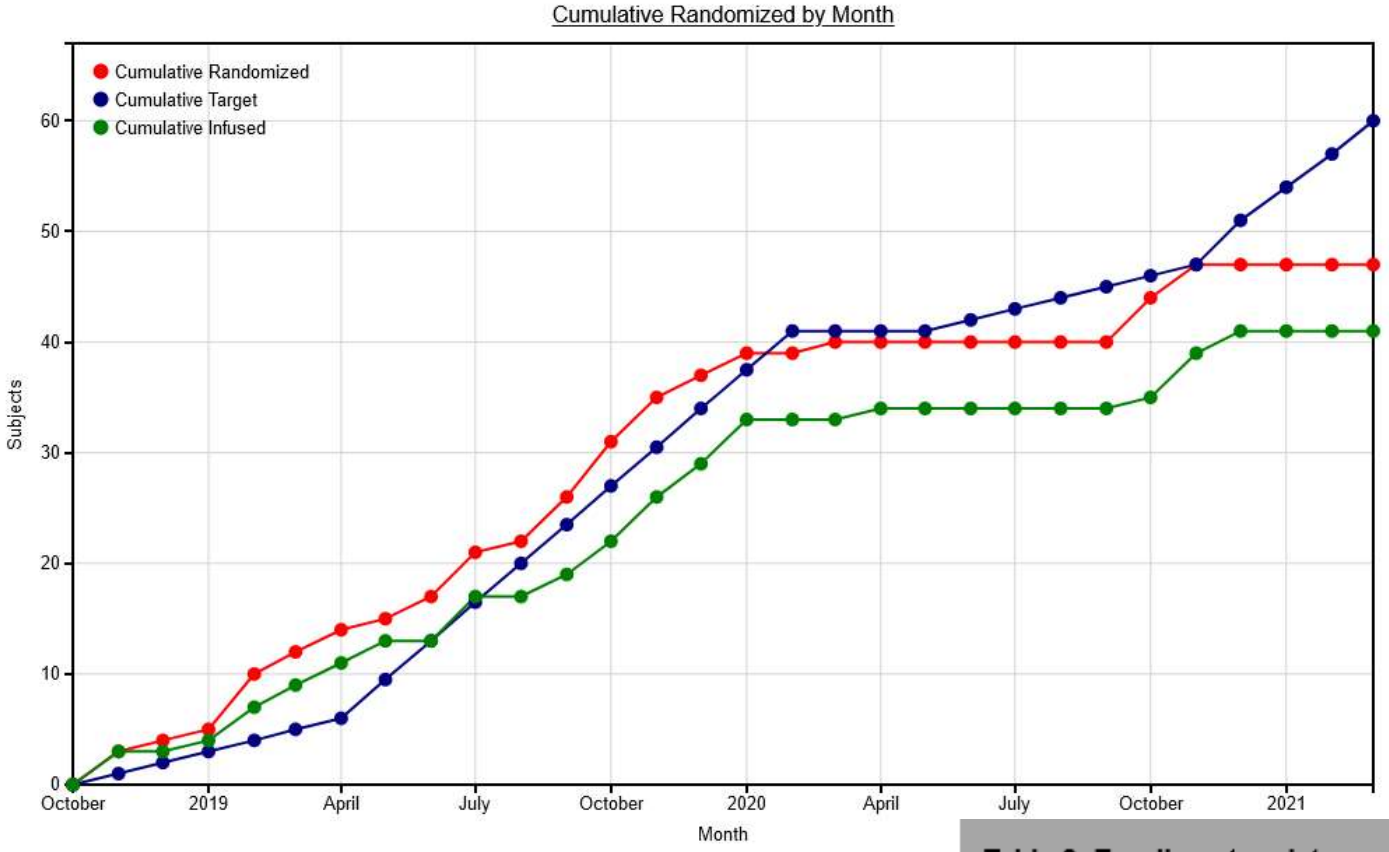


Table 2: Enrollment update	N
Target/Treated	81/41
Randomized	47
Treated	41
Randomized but not treated	6
Active in study	14
Completed study	26
Consent Withdrawn	1

MSCs in SLE
Trial Protocol Overview

- A Phase II sequential dose-escalation study evaluating the safety and efficacy of allogeneic umbilical cord derived mesenchymal stem cells (MSCs) for the treatment of adults with treatment refractory systemic lupus erythematosus (SLE).
- IND 16377 (sponsor: Gary Gilkeson, MD)

Primary Objective

- Test the hypothesis that SLE patients receiving the MSC infusion will respond better than patients receiving the placebo infusion when added to standard-of-care (SOC) therapy for moderate-severe active SLE.
- The primary endpoint will be clinical response at Week 24 as measured by reduction in disease activity using validated SLE-specific instruments, and maintenance by Week 20 of corticosteroid dose to ≤10 mg/day of prednisone or equivalent (for patients who require corticosteroids).

Secondary Objectives

- Additional endpoints include:
  - SAFETY:
    - Adverse events (AEs) between groups, including any serious AEs (SAEs), deaths
  - EFFICACY:
    - SLEDAI and BILAG changes between treatment groups
    - SLICC Damage Index changes
    - Steroid-sparing effects
    - Changes in patient-reported quality of life, fatigue, pain and depression
    - Changes in cellular, serum and urine biomarkers of SLE activity
    - MSC dose comparisons
  - MECHANISTIC STUDIES
    - Changes in number and activity of T regs, B and T cell activity markers, plasma cell numbers – compared between treatment groups
    - HLA Class I and Class II type differences between the MSC lines and the study participant's cell lines; development of anti-HLA antibodies

Guidance for Virtual Visits

- It is possible to score both the BILAG and the SLEDAI via a video visit with some caveats. We acknowledge that neither instrument is validated for video visits but based on today's circumstances, we believe it is best to proceed with scoring via video visits.

- Three aspects of the BILAG require they be observed to be scored
  - A) severe arthritis; B) severe rash; C) severe mucosal ulcerations.
  - To score any of these they have to be observed on a video visit and/or documented in a photograph.

- Please document on the Physical Exam CRF what you are able to observe at the visit.
  - If you are scoring a BILAG or SLEDAI category as present, either document it on the Physical Exam or provide in the Comments section what was observed or described that led you to score an item.
  - If you score arthritis on SLEDAI then you either have to describe it in the physical exam or explain in the comments section why it was scored.

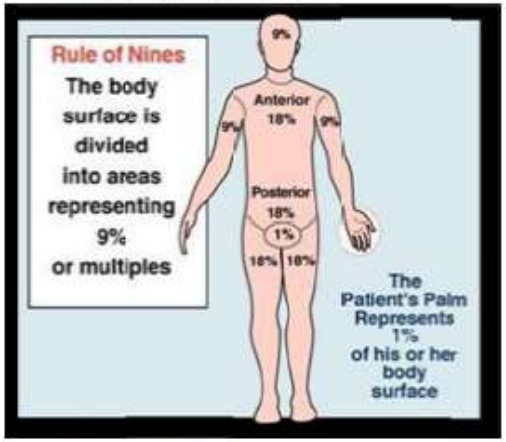
- On the BILAG there are a number of categories that we cannot ascribe at a video visit, but many of them we cannot ascribe for in person visits either, including most of the ocular findings.
  - Scoring those should be based on a report from an ophthalmologist or other medical specialist depending on the type of involvement.
  - You can mark things as negative if the patient has no complaints in that area and you feel comfortable marking it as absent.
  - It is impossible obviously to determine splenomegaly or lymphadenopathy via video unless it is serious swelling. We would recommend marking it as not present unless by history you suspect it is present which should be confirmed on the video, via a photo or at a subsequent face to face visit.

Guidance for Virtual Visits

- Completing the Physician Global Assessment during Times of COVID:
- The designated paper PGA form and designated ruler should be used when available, since they were calibrated at the start of the trial (with the printed line measuring exactly 100 mm, lining up with the rulers). But during COVID19 we are allowing sites to skip the designated paper PGA form with a PGA printed on regular paper.
- Ideally the print-out should be close in size to the original PGA (scaled at 100%). But since it will likely not be 100 mm in length, you can use any ruler and measure the mark and measure the line and make the conversion (here is an online calculator, but would also document the math on the source in the binder: https://www.ginifab.com/feeds/cm_to_inch/scale_converter.html).
- If you only measure to the mark on the printed paper it likely won't be correct, so make sure you are accounting for the overall length of the line and making the mathematical conversion.
- The measurements should be done on paper (not on a screen).

BILAG / SLEDAI Example

5. Severe eruption	> 18% body surface area any lupus rash except panniculitis, bullous lesion & angio-oedema body surface area (BSA) is estimated using the rules of nines (used to assess extent of burns) as follows: palm(excluding fingers) = 1% BSA each lower limb = 18% BSA each upper limb = 9% BSA torso (front) = 18% BSA torso (back) = 18% BSA head = 9% BSA genital (male) = 1% BSA
6. Mild eruption	≤ 18% body surface area any lupus rash except panniculitis, bullous lesion & angio-oedema malar rash must have been observed by a physician and has to be present continuously (persistent) for at least 1 week to be considered significant (to be recorded)



RASH

Definition: Ongoing inflammatory lupus rash.

A rash is scored if it is ongoing, new or recurrent. Even if it is identical in terms of distribution and character to that observed on the last visit and the intensity is improved, it is counted. Therefore, despite improvement in a rash, if it is still ongoing it represents disease activity. The rash must be attributable to SLE. A description of the rash must appear in the physical exam and should include distribution, characteristics such as macular or papular, and size.

The following should not be scored:

1. Chronic scarred discoid plaques in any location.
2. Transient malar flush, i.e., it is not raised and is evanescent

A common problem one may encounter is the differentiation between scoring a lesion as "rash" and/or "vasculitis". If a lesion meets the descriptive criteria of the latter it should not also be counted as rash, i.e., the score would be 8 points not 10 points. If a separate rash characteristic of SLE is present only then would "rash" also be scored.

COVID-19 Visit Impact Form

	Visit conducted	○ No ○ Yes
If Q26 is 'Yes'	Type of visit	○ Telephone ○ Video call ○ Home visit ○ Clinic visit
	Visit specifics *Provide details of how the visit was conducted.*	
	Visit conducted out of window *Derived by WebDCU.*	○ No ○ Yes
If Q03 is 'Yes'	Number of days out of window *Derived by WebDCU.*	_____ days
If Q26 is 'Yes'	PROMIS assessments conducted *PROMIS Emotional Distress-Depression, PROMIS Fatigue, PROMIS Pain Interference.*	○ No ○ Yes
If Q05 is 'Yes'	Alterations made in collecting the PROMIS instruments	
If Q26 is 'Yes'	SF - 36 conducted	○ No ○ Yes
If Q07 is 'Yes'	Alterations made in collecting the SF - 36	
If Q26 is 'Yes'	LupusPRO assessment conducted	○ No ○ Yes
If Q09 is 'Yes'	Alterations made in collecting the LupusPRO	
If Q26 is 'Yes'	Lupus Impact Tracker assessment conducted	○ No ○ Yes
If Q11 is 'Yes'	Alterations made in collecting the Lupus Impact Tracker	
If visit is not Week 1 or 2	SLEDAI and BILAG conducted	○ No ○ Yes
If Q13 is 'Yes'	Alterations made in collecting the BILAG and SLEDAI	
If Q26 is 'Yes'	PGA assessment conducted	○ No ○ Yes

Alterations made in collecting the PGA by the participant or physician	
Additional comments regarding assessments	
Blood sample collected	○ No ○ Yes
Urine sample collected	○ No ○ Yes
Mechanistic lab samples collected	○ No ○ Yes
Shipping of samples to Emory and/or MUSC postponed	○ No ○ Yes
Method of sample storage	
Any lab draw completed at an outside laboratory	○ No ○ Yes
Name of laboratory(s)	
Regulatory documents for external laboratory(s) *Upload a PDF of the CAP,CLIA, and reference ranges for any external lab used*	
Any adverse events identified	○ No ○ Yes
Reason visit was not conducted	

Study Arms

- After all eligibility criteria have been met, subjects will be randomized in a 2:1 ratio to receive either MSCs or placebo infusions. At the Baseline (Day 0) visit, subjects will receive 1 of 2 treatments, with the dose of active MSCs being dependent on the Cohort:

- Dose Cohort 1 (n=41)
  - Treatment Arm 1 (Active): **MSCs 1 x 10^6 cells/kg** given as a single infusion in Plasma-Lyte A solution + SOC
  - Treatment Arm 2 (Placebo): Placebo MSC Infusion (Plasma-Lyte A solution) + SOC.
  - Active and placebo bags are indistinguishable in appearance
- Dose Cohort 2 (n=40)
  - Treatment Arm 1 (Active): **MSCs 5 x 10^6 cells/kg** given as a single infusion in Plasma-Lyte A solution + SOC
  - Treatment Arm 2 (Placebo): Placebo MSC Infusion (Plasma-Lyte A solution) + SOC

Trial Design

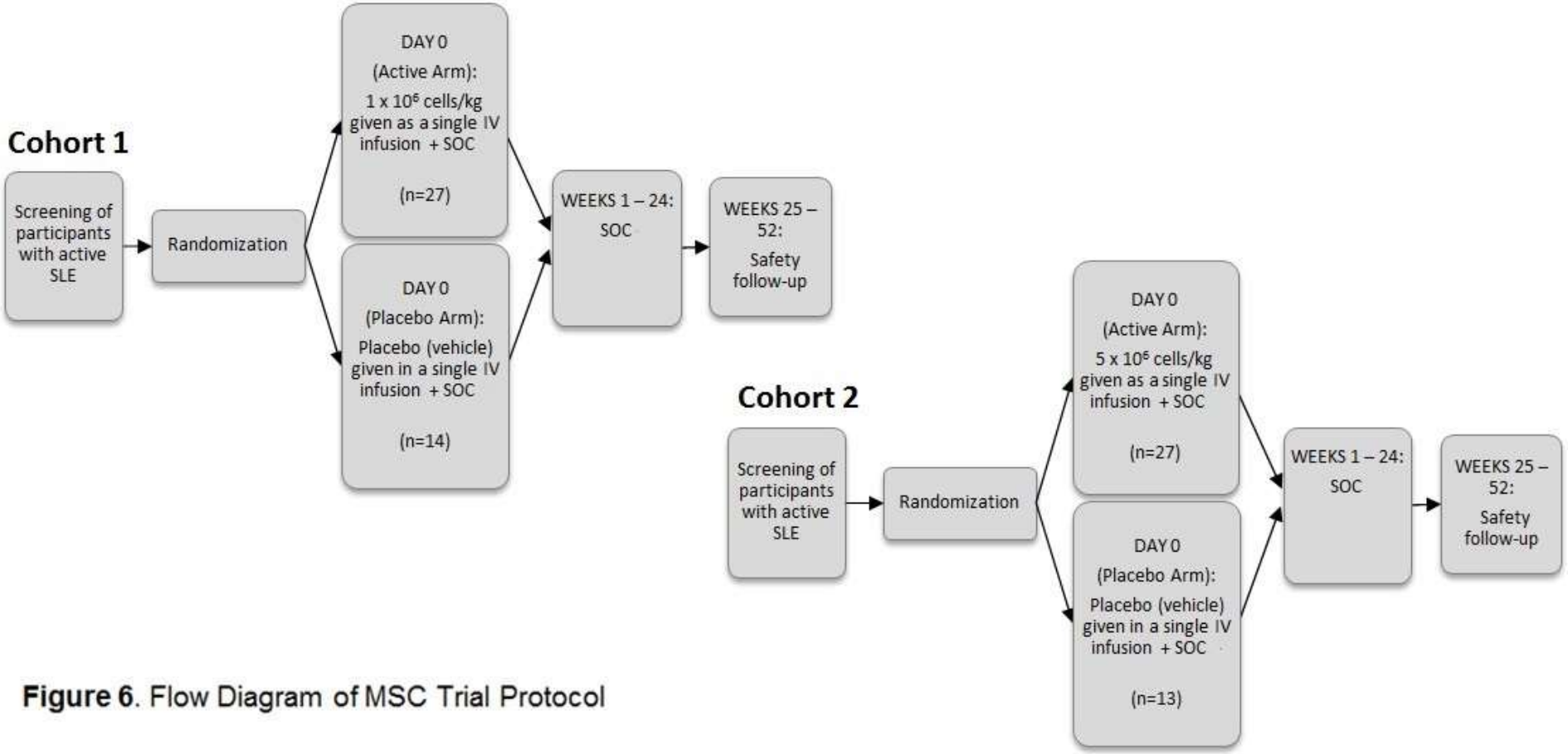


Figure 6. Flow Diagram of MSC Trial Protocol

Study Population

- Target population: Patients with **active SLE** disease (as opposed to stable disease or inactive disease).
  - The inclusion of patients with both a SLEDAI score of at least 6 and at least one BILAG A or BILAG B will ensure that patients with stable disease and inactive disease are not included.
  - The rationale behind including patients with SLE who have the SLEDAI score of at least 6 but just one BILAG B (such as active inflammatory arthritis that meets criteria for BILAG B but not A severity) is to be inclusive of patients with moderately active disease who are refractory to their current therapy.
- One limitation of this strategy is the narrow window of time in which to screen and enroll these patients before changes are made to their SLE medication regimens, including most commonly an addition of or increase in corticosteroids.
  - Designed so that all the patients enrolled are **allowed to receive corticosteroids, either newly initiated or increased in dose, up to 0.5 mg/kg/day** for their active disease in addition to the study intervention (MSC or Placebo infusion).

Primary Endpoint

- Clinical Response at **Week 24** as defined by the SLE Responder Index (SRI-4):

  1) a ≥ 4-point reduction in SLEDAI score,

  2) no new BILAG A or no more than 1 new BILAG B domain score, and

  3) no deterioration from Baseline in the physician's global assessment (PGA) by ≥ 0.3 points.

- Additionally, to be a "responder", corticosteroid dose must be tapered to ≤ 10 mg/day of prednisone or equivalent by **Week 20** (for patients who require corticosteroids) and be maintained at ≤10 mg/day through Week 24.

- Dose increases or new additions to SOC immunosuppressant therapy for SLE activity prior to Week 24 will be considered a non-response (i.e. failure). Discontinuing an immunosuppressant due to toxicity will be allowed. Any death will be considered non-response (i.e. failure).

Inclusion Criteria

1. Patients between 18 and 65 years old, male or female, of any race.
2. Historical presence of at least 4 of 11 of the ACR Classification Criteria.
3. Evidence of a positive ANA (≥1:80 titer by immunofluorescence) or positive dsDNA antibody test within 6 months of screening.
4. Clinically active SLE determined by SLEDAI score ≥ 6 and the presence of at least **one BILAG A or one BILAG B at screening**, despite standard-of-care therapy.
5. If BILAG A or B in the renal organ system, must have **completed at least 6 months of therapy for the current episode of nephritis** prior to Screening.
6. Able and willing to give written informed consent.

Protocol v5.0 Updates

- Incorporation of revised safety stopping rules
- Exclusion criteria modified to exclude active infections without a definitive treatment or patients who previously received IV MSCs
- Details added to clarify allowable timing of doses and indications of corticosteroids
- Change to allow rituximab, belimumab or other B cell depleting/modulating biologic therapy after Week 24
- Clarification of mITT to include "any" dosing of IP
- Added language for COVID-19 modifications
- 5.4 Prednisone Dosing:

Oral prednisone (or equivalent corticosteroid) up to 0.5 mg/kg/day will be allowed during the trial until Week 20, at which time the dose is required to be ≤ 10 mg/day and maintained ≤ 10 mg/day in order to meet the primary outcome by Week 24. Oral corticosteroid use >0.5 mg/kg/day for any indication will be a major protocol deviation until after the Week 24 visit. Intravenous and intramuscular administration of corticosteroids ~~is not allowed.~~ for any indication will be a major protocol deviation until after the Week 24 visit. Intra-articular, intra-bursal, tendon sheath and subcutaneous corticosteroid injections (presumably without systemic absorption) may be administered for conditions unrelated to active SLE throughout the duration of the trial. The determination that a condition is unrelated to active SLE will be made by the site principal investigator in consultation with the protocol chair and/or the medical monitor.

Protocol v5.0 Updates

- 5.5 Prohibited Medications:

All subjects are to have access to any care deemed medically necessary, but administration of any of the following medications are prohibited ~~while participating in this study~~until after the Week 24 visit unless otherwise specified, and will be considered major protocol deviations:

- Rituximab / Belimumab or other B cell depleting/modulating biologic therapy (until after the Week ~~52~~24 visit)
- Any experimental therapy (until after the Week 52 visit)
- Addition of any new immunosuppressant agent not part of the SOC regimen at the time of screening (until after the Week 24 visit). Following the Week 24 endpoint visit, doses of concurrent ~~non-biologic~~ immunosuppressive or immunomodulating drugs may be increased or new ~~non-biologic~~ immunosuppressive or immunomodulating drugs may be initiated for worsening disease manifestations.

- Revisions made to the Safety Stopping Guidance and Analysis Populations based on feedback from DAIT and the DSMB

COVID-19 Vaccination Timing

Medication	Timing Considerations for Immunomodulatory Therapy and Vaccination*	Level of Task Force Consensus
Hydroxychloroquine; apremilast; IVIG; glucocorticoids, prednisone-equivalent dose <20mg/day	No modifications to either immunomodulatory therapy or vaccination timing	Strong-Moderate
Sulfasalazine; Leflunomide; Mycophenolate; Azathioprine; Cyclophosphamide (oral); TNFi; IL-6R; IL-1; IL-17; IL-12/23; IL-23; Belimumab; oral calcineurin inhibitors; Glucocorticoids, prednisone-equivalent dose ≥ 20mg/day**	No modifications to either immunomodulatory therapy or vaccination timing	Moderate
Methotrexate	Hold MTX 1 week after each vaccine dose, for those with well-controlled disease; no modifications to vaccination timing	Moderate
JAKi	Hold JAKi for 1 week after each vaccine dose; no modification to vaccination timing	Moderate
Abatacept SQ	Hold SQ abatacept both one week prior to and one week after the first COVID-19 vaccine dose (only); no interruption around the second vaccine dose	Moderate
Abatacept IV	Time vaccine administration so that the first vaccination will occur four weeks after abatacept infusion (i.e., the entire dosing interval), and postpone the subsequent abatacept infusion by one week (i.e., a 5-week gap in total); no medication adjustment for the second vaccine dose	Moderate
Cyclophosphamide IV	Time CYC administration so that it will occur approximately 1 week after each vaccine dose, when feasible	Moderate
Rituximab	Assuming that patient's COVID-19 risk is low or is able to be mitigated by preventive health measures (e.g., self-isolation), schedule vaccination so that the vaccine series is initiated approximately 4 weeks prior to next scheduled rituximab cycle; after vaccination, delay RTX 2-4 weeks after 2nd vaccine dose, if disease activity allows	Moderate

RMD = rheumatic and musculoskeletal disease; IVIG = intravenous immunoglobulin; TNFi = tumor necrosis factor inhibitor; IL = interleukin; JAKi = janus kinase inhibitor; CYC = cyclophosphamide; RTX = rituximab; IV = intravenous; SQ = subcutaneous

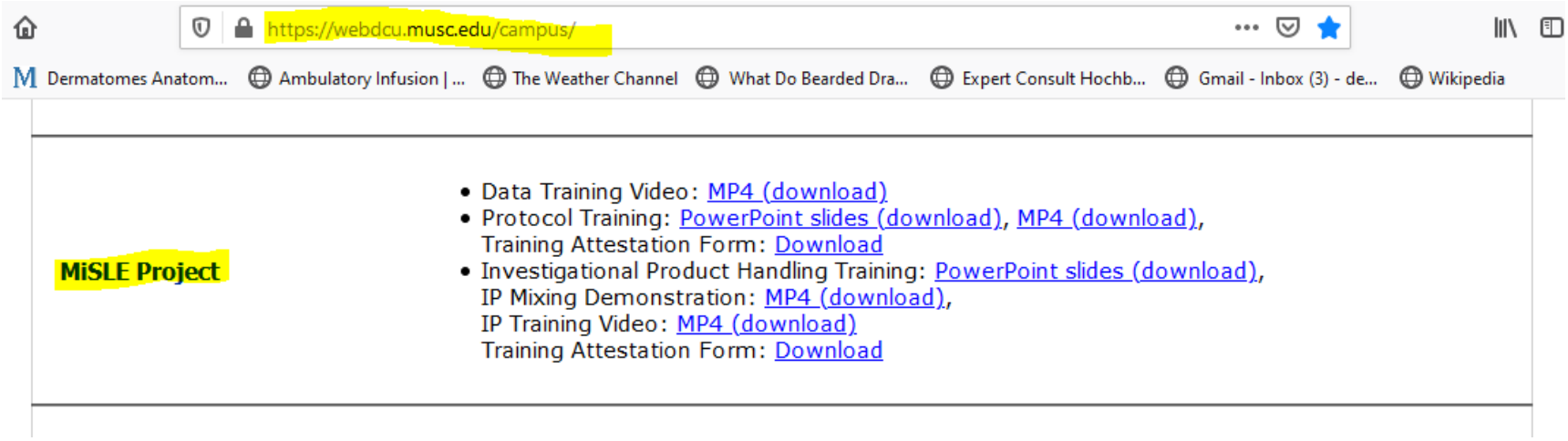
**guidance to 'hold' a therapy was made based on the assumption that the patient had well-enough controlled disease to allow for a temporary interruption; if not, decision-making should be determined on a case-by-case basis, considering the circumstances involved*

***consensus was not reached for vaccination timing in patients receiving prednisone-equivalent doses ≥ 20mg/day; see full guidance document, when published, for additional details*

Study Visit Schedule

	Screening (Day -28 to Day -1)	Baseline (Day 0)	Week 1, 2	Week 4, 8, 12	Week 16, 20	Week 24	Week 36	Week 52
Visit Window			+/- 2 days	+/- 1 week			+/- 4 weeks	
Written informed consent	X							
Inclusion/Exclusion criteria reviewed	X	X						
History and Demographics obtained	X							
Physical Exam & Review of Systems performed	X	X	X	X	X	X	X	X
Vital Signs obtained	X	X	X	X	X	X	X	X
SLEDAI, BILAG, PGA completed	X	X		X	X	X	X	X
SLICC-DI completed		X				X		X
SF-36 v2, PROMIS Fatigue, Pain & Depression SFs LupusPRO, LIT		X		X	X	X	X	X
Laboratory (CBC, CMP, C3, C4, anti-dsDNA, UA, urine protein:creat)	X	X	X	X	X	X	X	X
Laboratory (HIV, Hep B, Hep C, CMV, TB screen)	X							
Serum Pregnancy Test	X							
Urine Pregnancy Test		X	X	X	X	X	X	X
Mechanistic studies		X		Weeks 4 & 8 only		X		
Optional Specimen Collection (requiring additional consent)		X		X	X	X	X	X
CXR	X							
EKG	X							
Study Infusion (blinded)		X						

MiSLE Trial Training Videos



MiSLE Trial "Hotline"

- If in doubt, please call / text or email us!
  - Gary Gilkeson: Cell # 843-670-3667 gilkeson@musc.edu
  - Diane Kamen: Cell # 843-670-0767 kamend@musc.edu

Other Updates

- Randomization and Baseline Visit Procedures: Angela Brown (20min)
  - Process for handling of the cells, IP documentation, & personnel designations
- WebDCU: April Williams (30min)
  - Answering queries & entering data in a timely fashion
    - If a site falls behind, they will be required to attend a meeting with the study team to address any issues
  - AE Reporting
    - Reporting SAEs/BILAG A flares within 1-day window (end of next business day)
  - Lab Kits
    - Review of Lab Kit Tracking Module
    - Batch shipping boxes are to be provided by the sites per their site budget
- NIAID Updates
- PPD Updates
- Wrap up / Q&A (10min)

Thank You!
Any Questions?

MiSLE Investigators Meetings, Charleston SC Feb 2015 & Jan 2018