STUDY PROTOCOL

Project Name:

OPEN-LABEL STUDY OF TOFACITINIB FOR MODERATE TO SEVERE SKIN INVOLVEMENT IN YOUNG ADULTS WITH LUPUS

Sponsor:	Hermine Brunner, MD
Coordinating Center:	PRCSG staff
Investigational Medicinal Product/s:	Tofacitinib
Clinical Trial Working Full Title:	A 3-part open-label study assessing safety, tolerability, pharmacokinetic and -dynamic profiles, and efficacy of tofacitinib in young adults from age 18 to 45 years with moderate to severe skin involvement due to lupus

Version Date:

V19 20210322

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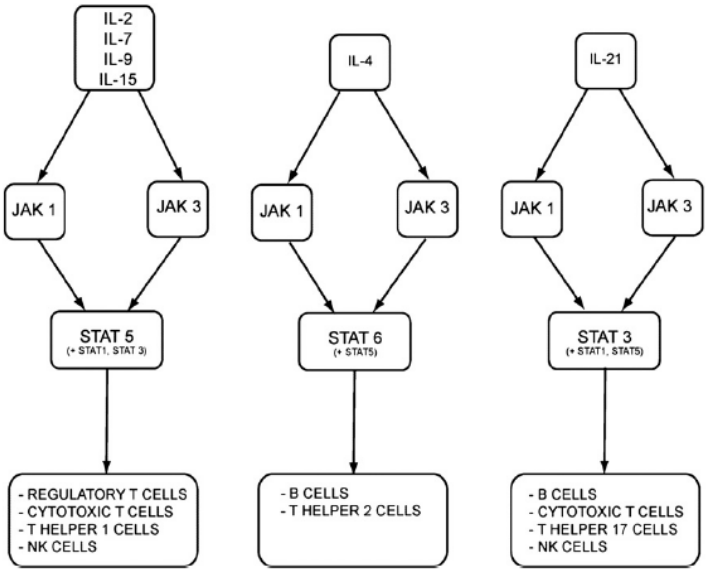
Abbreviations

BILAG	British Isles Lupus Assessment Group index
CLASI	Cutaneous Lupus Disease Area and Severity Index (appendix 5)
CS	Corticosteroid
ESR	Erythrocyte sedimentation rate
JIA	Juvenile Idiopathic Arthritis
PD	Pharmacodynamics
PK	Pharmacokinetic
SAE	Serious adverse event
SLE	Systemic lupus erythematosus
SLEDAI	SLE Disease Activity Index
SLE-CL	SLE cutaneous lesions
SOC	Standard of clinical care
TOFA	Tofacitinib
SC-RNA SEQ	Single-cell RNA sequencing of skin
TD1	Trial day 1

1. Rationale of Trial

Janus Kinases (Jak) are tyrosine kinases (Jak1, Jak2, Jak3 and Tyk2) that bind to cell receptor subunits and mediate the intracellular signalling initiated by interferons (IFN), many interleukins, colony stimulating factors, and hormones such as prolactin, erythropoietin and growth hormone. Following receptor ligation, Jak becomes activated and phosphorylates the latent transcription factors known as signal transducers and activators of transcription (STAT). Then STAT, in homo- or heterodimers, translocate into the nucleus and co-/regulate gene transcription. Mutations of Jak or STAT in humans are associated with severe immune dysfunction, revealing the fundamental role of this pathway in the induction and regulation of immune responses [1] (see Figure below).

Tofacitinib (TOFA), a small molecule that inhibits Jak3, Jak1 and to a lesser degree Jak2, has been proven efficacious in rheumatoid arthritis (RA) in phase III trials[2,3]. Notably, a series of Jak-STAT signalling cytokines, especially type I IFNs, IL-10 and IL-6, as well as the hormone prolactin, have been implicated in the pathogenesis of systemic lupus erythematosus (SLE)[4,5]. Such immunological abnormalities are thought to be even more pronounced among subjects with SLE onset early in life, i.e. with SLE diagnosis during childhood and adolescence[6]. In this context, targeting the Jak-STAT pathway may be an attractive approach to manage inflammation and auto-immunity in SLE.



The JAK-STAT signaling pathway. The IL-2 family of cytokines, all sharing a common receptor subunit γ-chain (γc), play a major role in promoting and maintaining T, B and natural killer (NK) cell populations. The IL-2 receptor family cytokines, after binding their receptor, activate the JAK/STAT signaling pathway. At the cytoplasmic side of the receptor, either JAK1 or JAK3 is phosphorylated. Activation of JAKs (~130 kDa) leads to attraction of a specific combination of STATs (70–94 kDa). IL-2, IL-7 and IL-15 are essential for T cell memory homeostasis, proliferation and survival, while IL-2 and IL-15 are important for NK cell development. IL-2 additionally regulates the homeostatic maintenance of Tregs and their function, and stimulates IFN-γ production by T-cells upregulating the cytolytic properties of CD8+ cytotoxic T cells. IL-4 activates STAT6 and T helper 2 (Th2) development. IL-21, by activating STAT1 and STAT3, induces differentiation of B cells into plasma cells and stimulates cytotoxic T cell proliferation. IL-21 also has regulatory effects, inhibits the antigen-presenting function of dendritic cells (DC), and is a pro-apoptotic factor for NK cells and incompletely activated B cells.

To date, belimumab, hydroxychloroquine, chloroquine and quinacrine are approved for adults with *systemic lupus erythematosus (SLE)*. The latter three medications are approved also for cutaneous lupus without the system form of the disease, i.e. SLE.

Despite these medications, chronic skin disease remains a major problem with SLE[7]. Given the severity of the disease, the unmet medical need, and the low number of available subjects in this specific population, it is judged acceptable to assess the safety, tolerability and PK as primary objectives; and efficacy as secondary objectives in an open-label manner. Subjects with *SLE-cutaneous lesions (SLE- CL)* will be treated with stable standard of care background for SLE and TOFA will be added to treat associated active cutaneous lesions with SLE, based on observed improvement of inflammatory rashes in previous trials of TOFA in various populations. Isolated cutaneous lupus erythematosus without SLE in adults is less common than in older adults and will not be studied[8].

With respect to SLE-CL, there is an ongoing clinical trial of TOFA in systemic SLE (NCT02535689) where adults with systemic SLE are dosed 5 mg BID. Further, there are several studies supporting the efficacy of TOFA in immune mediated alopecia as can occur with SLE-CL[9,10]. Studies in children with *Juvenile Idiopathic Arthritis* (JIA)[11] suggest that TOFA is well tolerated. Overall, patients found the taste of the TOFA oral suspension to be acceptable (see abstract poster presentation 388 from 2016 ACR meeting[12] (see Appendix 1).

2. Study Design

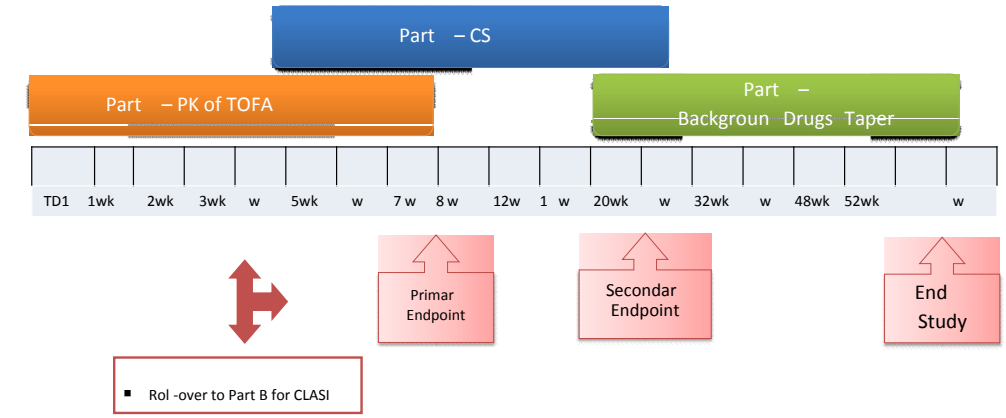
A scheme of the study design and flow is shown in the ***figure on the next page.***

This 76-week, 3-part Phase 1b/2 study is intended to evaluate the pharmacological properties (pharmacokinetics and pharmacodynamics), safety, tolerability and preliminary effectiveness of TOFA administrated to young adults (18-45 years) with moderately to severely active SLE-CL. Subjects will be studied at Cincinnati Children's Hospital Medical Center (CCHMC) and Metrohealth Medical Center.

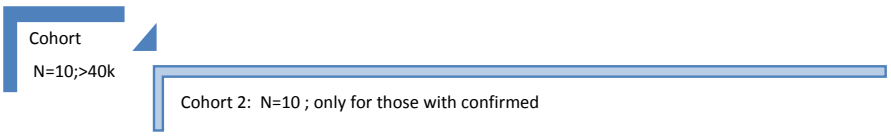
- **Part A** (up to week 8) requires stable background medications;
- **Part B** (up to week 24) allows for tapering of *corticosteroids (CS) in the setting of significant clinical improvement of SLE-CL as defined by a decrease in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI*) activity score by ≥50% from baseline *,* and
- **Part C** (until week 76) permits tapering of other background medications in subjects with clinical remission of SLE-CL (CLASI activity score=0). TOFA dosing is kept stable during Part C.

Cohort 1 (n=10, weight > 40kg and age ≥ 18 years and ≤ 45 years) will undergo intense PK-sampling to determine exposures following TOFA dosed at 5 mg BID. TOFA dose escalation will not be considered for inadequate response of SLE-CL.

Cohort 2 (n=10, weight > 40kg and age ≥ 18 years and ≤ 45 years) will be treated with the same dose as Cohort 1. No PK sampling will occur for Cohort 2.



Enrollment



All subjects discontinuing the study after TD1 will enter a 10-Week follow-up period (not shown in figure). TOFA – tofacitinib; study visits at trial day 1 (TD1), day 5 of week 1 ***for Cohort 1 only****. Subjects will be discontinued for toxicity or lack of response to TOFA at week 8.*

3. Trial Periods -Design

It is planned to enroll a total of 20 subjects aged 18 to 45 years with a body weight of > 40 kg with active SLE-CL that is not controlled by current standard of care medications at tolerable dosages.

Cohort 1 will undergo intense PK-evaluations during the **Intense PK Period of Part A**.

As shown in the figure above, subjects move from Part A to Part B to Part C of the study, unless they are discontinued from the study (see rescue clause, Section 6.5).

It is anticipated that almost all subjects will be treated with stable background therapy with an antimalarial (hydroxychloroquine, rarely chloroquine), up to 80% are treated with corticosteroids (CS), and about 50% of the subjects will also be treated with a non-biological DMARD (mostly methotrexate, azathioprine and mycophenolate mofetil) for prior multiorgan involvement with SLE.

Screening period

Duration up to 4 weeks; however, subjects should have the TD1 visit as soon as possible after the eligibility for the study has been confirmed.

In the event that a laboratory result does not meet inclusion/exclusion criteria for the study, the lab work may be repeated once in the four week period prior to the baseline visit to establish elibility for the study.

If the subject fails screening for the study, they may be re-secreened one time after the screen failure with permission from the sponsor. Subject will retain the same subject number as assigned at the initial study visit.

If a patient discontinues before the baseline visit, only the demographic information and inclusion/exclusion criteria with the primary reason for discontinuation should be completed on the eCRF. It is not necessary to complete all the required evaluations at the time of discontinuation unless medically indicated.

Part A (TD1 – week 8)

The primary objective of Part A is to characterize the PK of TOFA at the 5mg dose based on Cohort 1 data. Standard of care (SOC) therapies are kept stable during Part A. All background medications, including CS remain unchanged.

Cohort 1

Intense PK Period: PK sampling will only be done for subjects in Cohort 1. Starting at TD1, subject will be monitored at least weekly. PK sampling will occur pre-dose on Day 5 (approximately 11-13 hours after the second dose on Day 4) and 0.5, 1, 2, 4 and 8 hours post first dose on Day 5.

Cohort 2

Only if ≥ 1 subject of the Cohort 1 patients has shown partial response of SLE-CL to TOFA by week 4, will **Cohort 2** be enrolled.

Cohort 2 subjects will be seen in weekly intervals during Part A.

Cohort 1 and 2 subjects with clinical remission of SLE-CL can enter Part B as early as week 4 post baseline. Subjects who move from Part A to Part B prior to Week 8, will still be evaluated using the same visit schedule as subjects remaining in Part A until week 8.

Part B (week 8* – 24)

The primary objective of Part B is to assess safety and tolerability of TOFA, secondary objectives include effectiveness. Specifically, the PK of TOFA at the 5 mg dose based on Cohort 1 will be characterized.

- If CS are primarily given for SLE-CL, then CS may be decreased for clinically significant improvement as defined by a *Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI*) activity score by ≥50% from baseline and must be tapered for CLASI activity scores of 0 for > 2 months.

* Roll-over subjects in SLE-CL clinical remission may enter Part B as early as week 4

- If CS are mainly prescribed for other SLE manifestations besides SLE-CL, then CS can be decreased as per the investigator's decision, based on clinically significant findings of improvement.
- If the subject has been discontinued from CS and continues to be in SLE-CL clinical remission (CLASI activity score = 0), then the subject can enter Part C.

Subjects who move from Parts B to Part C prior to Week 24 will still be seen using the same visit schedule as subjects remaining in Part B until week 24.

Part C (week 24† – 76)

During Part C all therapies can be altered, per investigator discretion, with the exception of TOFA. The TOFA dose will remain stable throughout the study. Subjects who exit Part A or B early due to SLE-CL improvement will remain in Part C until they have been in the study for a total of 76 weeks.

4. Study description

4.1 Primary Objective(s) & Endpoint(s)

Primary objective

Part A (Cohort 1 only):

- To evaluate the pharmacokinetic (PK) profiles of TOFA in young adults with SLE-CL who are on stable treatment for SLE

Part A (Cohort 1 and Cohort 2):

- To evaluate the safety and tolerability of TOFA in young adults with SLE-CL

Part B and C:

- To evaluate the safety and tolerability of TOFA in young adults with SLE-CL

Primary endpoints

Part A (Cohort 1 only):

- **Day 5:** AUC_{inf} and C_{max} of tofacitinib

Part B: At Week 24:

- Nature, severity, and frequency of adverse events
- Incidence and severity of laboratory abnormalities

† as early as week 8 for subjects with clinical remission of SLE -CL and off CS

4.2 Key Secondary Objective(s) & Endpoint(s)

Secondary objectives

- To evaluate the efficacy of TOFA with SLE-CL over time compared to baseline

Secondary endpoint

Part A and B:

- Proportion of subjects that achieve a skin response (complete or partial response) as per the validated (CLASI) at weeks 4, 8 and 24 compared to baseline at TD1[14]. Response is defined as follows:
    - *Complete response (CR*) : complete resolution of the inflammatory rash (CLASI activity score = 0);
    - *Partial response (PR)*: ≥ 20% improvement of the CLASI activity score. A partial response (PR) is considered clinically significant
    - *No response:* < 20% improvement or even worsening of the CLASI activity score
    - *Cutaneous relapse: a new CLASI activity score* ≥4 in those subjects who previously achieved CR of SLE-CL (CLASI=0)

4.3 Exploratory Objective(s) & Endpoint(s)

Exploratory objectives

Part A:

- To evaluate single cell expression patterns of skin biopsies of affected and non-affected skin with TOFA therapy
- To examine changes in interferon α/γ receptor, STAT phosphorylation patterns with TOFA therapy using immunohistochemistry
- To investigate mRNA expression patterns in peripheral blood upon treatment with TOFA with focus on interferon regulated genes

Parts B and C:

- To evaluate steroid sparing properties of TOFA for SLE-CL
- To evaluate TOFA effect of overall disease activity in SLE as measured by the SLEDAI and BILAG
- To evaluate effects of TOFA on quality of life as measured by the Skindex (appendix 4) and overall well-being

Exploratory endpoints at week 4, 8, 12, 24, 52, and 76

Part A: Pharmacodynamics (PD)

- PD parameters include assessment of inhibitory effect of TOFA on expression of IL-2 responsive target genes downstream of the JAK/STAT pathway, such as FOXP3, SOCS3, IL-2Rα, interferon -γ and granzyme B.

Parts B and C:

- Decrease of absolute dose of systemic CS from baseline
- Decrease of body weight adjusted CS dose from baseline
    - CS dosing is measured in prednisone-equivalents
- Proportion of subjects who discontinue systemic CS
- Proportion of subjects with cutaneous relapse
- Change of BILAG score from baseline[13]
- Absolute value and percent change in plasma: Complement C3 and C4d, autoantibodies (anti-dsDNA)
- Change in number of inflamed joints from baseline[14]
- Change in SKINDEX score from baseline[15]
- Change of CLASI damage score[16] from baseline
- Change in SLEDAI score at each time point
- Change in protein: creatinine ratio at each time point.
- Change in subject's overall well-being at each time point
- Change in subject's ESR
- Proportion of subjects with clinically important reduction in SLE activity at each time point, based on CRV changes compared to baseline
- Proportion of subjects with flare of SLE activity at each time point, as defined by the BILAG[17]

Data of subjects who enter Part B before week 8 and/or Part C before week 24 will be considered on a last-observation (LOC) carried forward basis for endpoints of Part A and B, respectively.

5. Study Participants

5.1 Inclusion Criteria

1. Male or female ≥ 18 years of age and ≤ 45 years of age and > 40 kg body weight.
2. Fulfilled at least 4 out of the 11 Classification Criteria for SLE by the time of screening[18].
3. Willing to give written informed consent, must fully understand the requirements of the trial, and must be willing to comply with all trial visits and assessments.
4. CLASI activity score of 8 or higher[19] at screening and baseline despite standard of care therapy.
5. Stable dose of prednisone of ≤ 20 mg/day within 2 weeks of enrollment.

6. Female subjects of childbearing potential must use a highly effective method of contraception to prevent pregnancy (abstinence is considered highly effective) and must agree to continue to practice adequate contraception for the duration of their participation in the trial and for 28 days after their last dose of TOFA.
7. Female subjects of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at Trial Day 1 before dosing.
8. For subjects receiving leflunomide treatment, total daily dose does not exceed 20 mg.
9. A negative QuantiFERON-TB Gold In-Tube test performed within the 3 months prior to screening, or within the screening period prior to baseline. A negative PPD test can be substituted for the QuantiFERON-TB.
10. Subjects either have protective varicella titers or evidence of having been vaccinated against varicella.

5.2 Exclusion Criteria

Subjects are not eligible for this trial if they fulfil any of the following exclusion criteria:

1. Mild SLE-CL defined as a CLASI activity score of 7 or lower at screening and baseline.
2. Increase in CS dosing within 2 weeks prior to Trial Day 1, or expected to require an increase in CS dosing during the first 4 weeks of the study.
3. Use of i.v. corticosteroids within 4 weeks prior to Trial Day 1.
4. Increase in dosing of methotrexate, leflunomide, within 4 weeks before Trial Day 1 or expected to require an increase during the first 8-weeks of the study.
5. Increase in dosing of hydroxychloroquine, or chloroquine within 4 weeks before Trial Day 1 or expected to require an increase during the first 8-weeks of the study.
6. Rituximab within 1 year of Trial Day 1.
7. Increase in dosing of any medication or herbal treatment considered to have immunosuppressive properties with 4 weeks before Trial Day 1.
8. Prior treatment with or known intolerability of TOFA.
9. Use of cyclophosphamide (i.v. or oral), cyclosporine, or tacrolimus within 12 weeks prior to Trial Day 1.
10. Treatment with other investigational agents within the last 6 months or 5 half-lives, or as per washout requirement from the previous protocol, whichever is longer.
11. Estimated glomerular filtration rate less than or equal to 60 mL/min /1.73 m2.
12. Known positive Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV), or Hepatitis B surface antigen (HBsAg) serology.

13. Any condition, including findings in the laboratory tests, medical history, or other screening assessments, that, in the opinion of the Investigator, constitutes an inappropriate risk or a contraindication for participation in the trial or that could interfere with the trial's objectives, conduct, or evaluation.
14. Active central nervous system SLE deemed to be severe or progressive and/or associated with significant cognitive impairment leading to inability to provide informed consent and/or comply with the protocol.
15. Significant renal disease due to a reason(s) other than Lupus Nephritis (e.g. diabetes mellitus, renovascular disease, or antiphospholipid syndrome).
16. Severely active Lupus Nephritis defined as a renal BILAG A score.
17. History of dialysis within 3 months prior to Trial Day 1 or expected to need during the trial.
18. History of or planned renal or other organ transplantation.
19. Known active clinically significant viral, bacterial or fungal infection, or any major episode of infection requiring hospitalization or treatment with parenteral anti-infectives within 8 weeks of screening, or completion of oral anti-infectives within 2 weeks of Trial Day 1.
20. Breastfeeding or currently pregnant.
21. Legal incapacity or limited legal capacity to provide informed consent or assent.
22. Blood dyscrasias, including:
    - Hgb <10 g/dL or Hct <33%.
    - WBC <3.0 x 10^9/L.
    - Neutrophil count <1.2 x 10^9/L.
    - Platelet count <100 x 10^9/L.
    - Lymphocyte count of <0.5 x 10^9/L.
23. AST or ALT > 1.5 times the upper limit of normal or any other clinically significant laboratory abnormality.
24. History of any other rheumatic autoimmune disease.
25. Infections:
    - Latent or active TB or any history of previous TB.
    - Chronic infections.
    - Any infection requiring hospitalization, parenteral antimicrobial therapy or judged to be opportunistic by the investigator within the 6 months prior to the first dose of study drug.
    - Any treated infections within 2 weeks.

- History of recurrent (more than one episode) herpes zoster or disseminated (a single episode) herpes zoster or disseminated (a single episode) herpes simplex.
- History or current symptoms suggestive of any lymphoproliferative disorder, including Cytomegaly Virus (CMV) or Epstein Barr Virus (EBV) related lymphoproliferative disorder, history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease.

26. Subjects taking potent and moderate cytochrome P450 3A4 (CYP3A4) inhibitors (see Appendix 2).
27. Subjects taking potent and moderate CYP3A4 inducers (see Appendix 2).
28. Subjects who have been vaccinated with live or attenuated vaccines within the 6 weeks prior to the first dose of study medication. All subjects should be up-to-date with respect to standard of care vaccinations (as defined by their country health ministry) as permitted by past immunosuppressive therapy for SLE.
29. Subjects with a malignancy or with a history of malignancy with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.
30. Subjects with a history or current diagnosis of diverticulitis.

6 Treatments, Regimens & Control

This is a 3-part study designed to evaluate the Pharmacokinetics and Pharmacodynamics of TOFA in young adults with active SLE-CL (CLASI activity score>8) aged 18 to 45 years. Safety and efficacy will be evaluated as secondary objectives. Subjects achieving CR of SLE-CL may be permitted to roll-over to subsequent parts of the study earlier.

In Part A (baseline – week 8), subjects will be enrolled in an open-label arm to receive TOFA orally twice per day. PK analysis will be performed on Cohort 1 only to measure PK parameters. Starting week 4, subjects may roll over from Part A to Part B early, if there is clinical remission of SLE-CL (CLASI activity score = 0).

In Part B (week 8 – 24), subjects will continue TOFA as in Part A but CS can be decreased for clinically significant improvement of SLE-CL by $\geq$ 50% from baseline. Subjects who maintain clinical remission of SLE-CL and succeeded in discontinuing CS, can roll over to Part C prior to week 24.

In Part C (week 24 – 76), subjects off CS who are in clinical remission of SLE-CL will be able to taper and change other background medications. TOFA dosage will remain stable.

It is planned to enroll:

Cohorts 1: n=10, weight > 40 kg age $\geq$18 up to and including 45 years.

Cohort 2: n=10; weight > 40 kg and age ≥ 18 years up to and including 45 years. Enrollment of subjects into Cohort 2 will commence once enrollment of Cohort 1 are completed.

6.1 Treatment

1. **Active drug**: TOFACITINIB (TOFA)
2. **Allowable background anti-inflammatory systemic SLE therapy includes**:

   a) Subjects on a stable dose of hydroxychloroquine for at least 1 month prior to study entry are permitted to continue use throughout the duration of the study with a maximum allowable dose of 400mg.

   b) Subjects are permitted ot continue the use of oral corticosteroids (CS), methotrexate (MTX), and leflunomide, at allowed doses, as well as NSAIDs and ASA.

6.2 Dosing

TOFA dosing: Twice daily orally

As documented in the TOFA Investigator brochure (Section 6.1; Version March 2016) doses up to 30 mg twice daily were safe and tolerated**.** However, for the purpose of this study only the dose of TOFA approved for rheumatoid arthritis (5 mg PO BID) will be tested.

Based on TOFA PK in the Rheumatoid Arthritis (RA) population [body weight (BW) ranging from 40 kg - 140 kg)], clearance (CL) of TOFA is not dependent on body weight in adult subjects. Thus, the starting dose of TOFA will be 5 mg orally twice daily, an approved dose of TOFA in adult RA subjects in most countries. Dose excalation will not occur even with lack of SLE-CL improvement.

Corticosteroids (CS):

At study entry, CS dosage must be ≤ 20mg/day. CS should be kept stable up to and including week 4.

CS can be decreased starting week 5:

- CS may be decreased for improvement of the CLASI activity score by ≥50% from baseline and must be tapered for CLASI activity scores of 0 for > 8 weeks (or 2 subsequent study visits, whatever is shorter), provided CS are mainly prescribed for SLE-CL. This will minimize morbidity associated with CS use as much as possible.
- If CS are mainly prescribed for other SLE manifestations besides SLE-CL, then CS can be decreased as per the investigator's decision, even in the setting of complete response of SLE-CL, based on continued improvement of clinical findings of SLE.

Oral CS may be increased above the baseline level up to max of 60 mg/day for new BILAG A or B flares in organ systems other than mucocutaneous organ system (i.e. neurologic, ophthalmologic, musculoskeletal, cardiopulmonary, gastrointestinal, renal, hematological organ systems) but must be returned to baseline dose or lower within 14 days. If this is not achieved then the subject is considered a treatment failure.

- Up to 3 doses of pulse methylprednisolone may be given for new BILAG A or B flares instead.
- CS increases can occur no more than 3 times during the duration of the study, Part A- C.
- Subjects requiring more than 3 CS increases will be withdrawn from treatment phase of study.

Other anti-inflammatory medications used as part of standard of care (SOC) for SLE

These include methotrexate (MTX) or leflunomide or mycophenolate mofetil, hydroxychloroquine (HCQ) or chloroquine (CQ), and NSAIDs, which are all allowed during the study. All background therapy dosages given prior to Screening must have been kept stable according to the specifications in the exclusion criteria for a subject to be eligible for the study. These medications must remain stable during the Screening period and Part A. SOC medications are part of the subject's previous SLE treatment and thus will not be provided by the Sponsor.

Other permitted Medicine

Vitamin D (≥ 400 IU/day) and calcium supplements (≥ 800 mg/day) may be given for prevention of glucocorticoid-induced bone loss (ACR Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis, 2001).

Paracetamol (acetaminophen) may be initiated for pain control of SLE symptoms during the study. This should be titrated off as tolerated, and preferably not taken on the day of the clinic visit. Other pain medications, including opiates, may be used for temporary relief of symptoms not due to SLE.

Vaccines

Subject should be as up to date with childhood vaccinations as much as previous SLE treatments permitted. It is recommended that subjects be vaccinated against infectious diseases according to the local standard of care (i.e. influenza, pneumococcal vaccine, varicella), preferably at least 2 weeks before TD1. It should be noted that live and live-attenuated vaccines are not authorized within 6 weeks before TOFA intake, during the trial period, and for 6 weeks following the last dose of TOFA.

6.3 Controls

The primary objective of this PK bridging study is safety and tolerability, and thus it is acceptable to avoid the use of placebo.

6.4 Total duration

76 weeks (part A through C) or until TOFA is considered no longer needed by the investigator, whichever is first.

6.5 Rescue clause, treatment failure & subject withdrawal

A subject will be considered a treatment failure and discontinued from the study if he/she experiences one or more of the following:

- Serious adverse event that is possibly related to TOFA;
- Important worsening of renal disease defined as a persistent increase in proteinuria as measured by the protein: creatinine (PC) ratio to values > 2.0 after achieving complete response of lupus nephritis, or doubling of proteinuria with values PC ratio >3.0 after achieving a partial response of lupus nephritis;
- Need to increase current or initiation of new SLE background therapy due to non-renal SLE manifestations;
- Life-threatening SLE complications as judged by the investigator;
- Need for more than the protocol defined allowable CS rescue therapy as determined by the treating physician;
- No improvement of SLE-CL as measured by the CLASI by week 8;
- Two sequential absolute lymphocyte counts less than <0.5 x 10^9 or 500 cells/mm^3;
- Two sequential hemoglobin values <8.0 g/dL (80 g/L) or decreases greater than 2 g/dL on treatment;
- Female subjects that become preganant during the study will discontinue study treatment. They will be continued to be followed in accordance as outlined in section **7.3.10.**

Subject Withdrawal

Subjects may withdraw from the study at any time at their own/their legal guardian's request, or they may be withdrawn at any time at the discretion of the physician investigators for safety, behavioral, or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible.

The investigator will inquire about the reason for withdrawal, request the subject to return all unused investigational product, request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved AEs.

7 If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.Planned Assessments & Evaluations

7.1 Evaluations for ALL Subjects

PART A

Cohort 1: Subject will be monitored at Day 1 and Day 5 of week 1, and then once per week during weeks 2, 3, 4, 5, 6, 7, 8.

PK samples will be drawn on Day 5 of Trial Week 1: pre-morning dose and 0.5, 1, 2, 4 and 8 hours post-morning dose of Day 5.

Cohort 2: TD1, and then once per week during weeks 2, 3, 4, 5, 6, 7, and 8.

PART B‡

Subjects of Cohorts 1 and 2 will be monitored at study visits at weeks 10, 12, 16, 20 and 24. CS dosing can be changed during Part B.

PART C§

Subjects of Cohorts 1 and 2 will be monitored at study visits every 8 weeks until week 76. Background medications, CS and other background medications can be changed during Part C, while TOFA remains stable.

Follow-up Period

All subjects who discontinue TOFA treatment at any time post-baseline will have a follow up phone call 10 weeks after the last TOFA dose to monitor for the development of safety events.

7.1.1 Disease activity

- SLEDAI-2K and BILAG-2004 [17,20]
- Physician Global Assessment of SLE activity (visual analog scale ; 0-10)

‡ Roll-over subjects in SLE-CL clinical remission may enter Part B as early as week 4

§ as early as week 8 for subjects with clinical remission of SLE -CL and off CS

- CLASI Activity Score[16]

7.1.2 Patient-reported outcomes

- Well Being Assessment (visual analog scale ; 0-10)
- Pain (visual analog scale ; 0-10)
- SKINDEX-29 (appendix 4)[15]

7.1.3 Other outcome measures

- SLICC/ACR damage index[21]
- CLASI Damage Index[16]

7.1.4 Laboratory parameters

- ESR
- Hematology
- Clinical chemistry
- C3,C4, dsDNA-antibodies
- Urine PC ratio
- Quantitative EBV and CMV PCR

7.2 Evaluations Performed in Select Subjects

7.2.1 Photography & skin biopsy

A subset of up to 3-5 subjects from either Cohort 1 or Cohort 2 will be asked to participate in serial photography of lesions on the back, face or the extremities. Picture will be obtained three times during the study by a trained individual or medical photographer, starting from baseline (also see Schedule of Events).

Subjects agreeing to participate in photography will also be asked to consent to two skin biopsies. At each of the two biopsy sessions 2 skin samples will be obtained (approximately 3 mm in diameter) by means of punch biopsy. The first two skin biopsy samples will be taken from an active SLE-CL lesion located over the back or the extremities during week 1. The second two skin biopsy samples will be taken from the initial lesion, in close geographical proximity to the site of the initial biopsy, between weeks 8 and 15.

Prior to taking the skin biopsy the area will be numbed with topical or injectable lidocaine.

7.2.2 Pharmacokinetic parameters

Plasma TOFA levels

Cohort 1 will undergo intensive sampling in week 1.

7.2.3 Exploratory Pharmacodynamic Biomarkers

A subset of subjects will be asked to participate in translational research studies, performed 2 or 3 times during the study.

- Blood samples for RNA and miRNA level gene expression with focus on interferon regulated pathways
- Interferon γ and interferon α levels
- T cell activation of flow – C1 or POLARIS
- Urine biomarkers
- Single-cell RNA sequencing of skin cells
- Immunohistochemistry of skin cells for phosphorylated STATs and interferons

7.3 Safety & Adverse Event Reporting

Safety reporting will be completed in accordance with IRB guidelines and FDA requirements (21 CFR Part 312) for studies performed under an IND.

7.3.1. Adverse Events

All observed or volunteered *Adverse Events* (AE) will be reported as described in the following sections.

For all AEs, the site's investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a *Serious Adverse Event* (SAE) requiring immediate notification to the IRB and Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigators to determine the causality of the AE. The investigators will assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the IRB, the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Principal Investigator, any non-serious adverse event that is determined by the Principal Investigator (PI) to be serious will be reported by the PI as a SAE.

7.3.2. Reporting Period

For SAEs, the active reporting period to the IRB and Pfizer begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving TOFA, through and including 28 calendar days after the last administration of the investigational product.

SAEs occurring to a subject after the active reporting period has ended should be reported to the IRB, FDA, and PFIZER if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the IRB, FDA and PFIZER.

AEs (serious and non-serious) will be recorded on the CRF from the time the subject has taken at least one dose of study treatment through last subject visit.

7.3.3 Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure in Utero (EIU);
- Exposure via breast feeding;
- Medication error;
- Occupational exposure.

7.3.4 Infections

All treated infections occurring during the study, including, but not limited to, respiratory infections, cutaneous infections, urinary tract infections and episodes of suspicious or febrile diarrhea, should be cultured and any identified organisms noted

in the case report form (CRF). Infections should be classified as either serious infections or treated infections, as defined below.

Serious Infections

A serious infection is any infection that requires hospitalization for treatment or requires parenteral antimicrobial therapy or meets other criteria that require it to be classified as a serious adverse event. A subject who experiences a serious infection must be discontinued from the study. This infection must be reported as a serious adverse event and should be listed as the reason for discontinuation in the electronic case report form (eCRF). Appropriate laboratory investigations, including but not limited to cultures should be performed to establish the etiology of any serious infection. All adverse events, including serious adverse events, must be reported as described in Section 7.7.1 on Adverse Event Reporting.

Treated Infections

A treated infection is any infection that requires antimicrobial therapy by any route of administration or any surgical intervention (e.g., incision and drainage). A subject who experiences a serious infection must be discontinued from the study. This information must be noted in the eCRF.

7.3.5 Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or PI.

Merely repeating an abnormal test, in the absence of any of the above conditions, will not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

7.3.6 Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections and will be handled as SAEs in the safety database.

Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and will always be considered important medical events.

Subjects who subsequently present with AST or ALT ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase ≤2 X ULN or not available are asked to return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results.

This evaluation may include laboratory tests, detailed history and physical assessment. In addition to repeating AST and ALT, laboratory tests should include albumin, kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, creatinine prothrombin time (PT)/International Normalized Ratio (INR) and alkaline phosphatase.

A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, will be collected.

Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal liver function tests. Such potential Hy's Law cases should be reported as SAEs.

Study drug will be discontinued if liver injury is noted as defined above.

7.3.7 Hospitalization

AEs reported from studies associated with hospitalization or prolongation of hospitalization, are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g. from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (e.g., for work-up of persistent pre-treatment lab abnormality);
- Social admission (e.g., subject has no place to sleep);
- Administrative admission (e.g., for yearly physical exam);
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, will not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

7.3.8 Severity Assessment

If required on the AE CRFs, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

- MILD- Does not interfere with subject's usual function.
- MODERATE -Interferes to some extent with subject's usual function.
- SEVERE- Interferes significantly with subject's usual function.

A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

7.3.9 Causality Assessment

The investigator's assessment of causality will be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship will be provided.

If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the PI (see Section on Reporting Requirements).

If the investigator's causality assessment is "unknown but not related to investigational product", this will be clearly documented on study records. In addition, if the investigator determines an SAE is associated with study procedures, the investigator will be record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

7.3.10 Exposure In Utero

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with TOFA, the investigator will submit this information to the IRB, and the Pfizer Drug Safety Unit on a Serious Adverse Event Form and *Exposure in Utero* (EIU) Supplemental Form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (e.g., a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EIU Form.

This will be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information for all EIU reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination and notify Pfizer of the outcome as a follow up to the initial EIU Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise or a neonatal death]), the investigator will follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- "Spontaneous abortion" includes miscarriage and missed abortion.
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the EIU Pregnancy Partner Release of Information Form to deliver to his partner. The Investigator will document on the EIU Form that the subject was given this letter to provide to his partner.

7.3.11 Withdrawal Due to Adverse Events (See also section on Subject Withdrawal)

Withdrawal due to AE should be distinguished from withdrawal due to insufficient response, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws due to an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

7.3.12 Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

7.3.13 Reporting Requirements

Each AE is assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EIU and exposure during breast feeding cases. In the rare event that the

investigator does not become aware of the occurrence of an SAE immediately (e.g., if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

The IRB will be notified per institutional policy.

In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the IRB and Pfizer or its designated representative.

Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AE should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8 Planned Statistical Analyses

8.1 Pharmacokinetic Analysis

The PK concentration population is defined as all subjects enrolled and treated for whom at least 1 TOFA level or parameters of interest can be determined.

PK parameters of TOFA following multiple-dose oral administration will be derived from the concentration-time profiles using noncompartmental analysis. The observed predose concentration will also be used as the 12-hour concentration in these calculations, assuming steady state. Actual PK sampling times will be used in the derivation of PK parameters.

The plasma PK parameters from noncompartmental analysis (CL/F, Vz/F, AUCt, Cmax, Tmax, and $t_{1/2}$ (if data permit)) on Day 5 will be summarized descriptively by Visit/Day. Plasma concentrations will also be summarized descriptively by PK sampling time. Individual subject concentration-time data will be plotted using actual PK sampling times. Summary profiles (mean and median plots) of the concentration-time data will also be presented. Summary profiles will be presented on both linear-linear and log-linear scales.

The PK parameters such as CL/F and Vz/F may be compared with historical adult RA and JIA patients data using mixed effect modeling approach.

8.2 Safety Analyses

The safety population will be all subjects who received at least 1 dose of TOFA. No interim analyses are planned.

AE, SAEs and serious adverse events will be summarized using frequencies and under consideration of the number of study subjects affected. Further, in secondary analysis, we will use mixed model analysis to assess the relationship between side effects and (1) subject weight (2) background therapy with CS; (3) concurrent use of a nonbiological immunesuppressant,or (4) a history of lupus nephritis.

8.3 Effectiveness Analyses

Due to the small sample size, results may not show statistical significance. Statistical significance may not be reached in final data analysis. However, a trend towards improved clinical status may assist planning efforts of a larger clinical trial to assess efficacy.

The efficacy population will be all subjects who were enrolled in the study and received at least 1 dose of TOFA. No interim analyses are planned. We will perform intention-to-treat analyses, with the last observation carried forward in primary analyses; and will also perform analyses on observed data in secondary analyses. As this is an open-label study, no control group is available. Efficacy measures are listed under Section 7. Data of subjects who enter Part B before week 8 and/or Part C before week 24 will be

considered on a last-observation (LOC) carried forward basis for endpoints of Part A and B, respectively.

To assess the benefits of TOFA on skin manifestations of SLE, we will use descriptive analysis and contingency table analysis, using Chi-square and Fisher Exact test as appropriate, to determine the proportion of subjects who are partial or complete CLASI responders at weeks 4, 8 and 24 compared to baseline. To assess the effect of TOFA on skin damage, we will compare the change (increase) of CLASI damage score[16] from baseline to the end of Part B and C, respectively, using paired T-tests.

To assess the steroid –sparing properties of TOFA, we will determine the proportion of study subjects who can discontinue steroids at the end of Part B and C, respectively. We will also evaluate steroid sparing properties of TOFA for SLE-CL by comparing steroid doses (absolute and weight-adjusted) at baseline with those in the end of Part B and C, using a paired T-test.

Similarly, we will assess TOFA effect of overall disease activity in SLE as measured by the numeric SLEDAI and BILAG scores, respectively. We will also perform sub-analyses and evaluate improvement or resolution of other organ-system activity (e.g. serological activity – measured by anti-dsDNA antibodies and low complement levels; joint counts) using paired T-tests and contingency table analysis, as appropriate. In a similar fashion the change of the other SLE core response variables (CRV) besides disease activity (SLEDAI, BILAG) will be assessed at each study visit.

To explore the effects of TOFA on quality of life, we will compare the SKINDEX score (appendix 4), well-being and pain assessments from baseline to the end of Part B and C, respectively.

We will also explore single cell expression patterns of skin biopsies of affected and non-affected skin with TOFA therapy; and examine changes in interferon α/γ receptor, STAT phosphorylation patterns with TOFA therapy using immunohistochemistry; we also explore mRNA expression patterns in peripheral blood upon treatment with TOFA with focus on interferon regulated genes.

We will also explore at week 4, 8, 12, 24, 52, and 76, the relationship of PD parameters: the inhibitory effect of TOFA on expression of IL-2 responsive target genes downstream of the JAK/STAT pathway, such as FOXP3, SOCS3, IL-2Rα, interferon (IFN)-γ and granzyme B will be studied.

9. Data Safety Monitoring Plan

This study follows procedures for minimizing risks and ensuring the safety and confidentiality of human subjects, as established under both the Department of Health and Human Services and the Office for Human Research Protections (OHRP). The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki and will be consistent with Good Clinical Practices (GCP) http://www.fda.gov/cder/guidance/959fnl.pdf and applicable regulatory requirements. A consent form describing all aspects of the study will be approved by the IRB. The nature of all possible treatment assignments, as well as their risks and potential benefits, will be fully explained to all participants. The study sites will take appropriate measures to ensure the confidentiality of the data and the well-being of the subjects. Medidata Rave will be used for Electronic Data Capture.

Please see Appendix 3 for a detailed Data Safety Monitoring Plan.

Considering the small size of the study and the substantial experience with tofacitinib use in humans (see IB; Appendix 3) no Data Safety Monitoring Board will be formed[23]

10 Schedule of Assessments

Trial Period	Screening	Part A								Part B					Part C						
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**
Trial Week	0	1[*1]	2	3	4	5	6	7	8	10	12	16	20	24	32	40	48	56	64	72	76/EOS
Time Windows	Day -30 to Day -1	Day 1	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day	±2 day	±2 day	±3 day	±3 day	±3 day	±5 day	±5 day	±5 day	±5 day	±5 day	±5 day	±3 day
Informed Consent	X																				
Inclusion/exclusion criteria	X	X																			
Medical history, medication	X																				
Tuberculosis assessment	X																				
Serum virology (HBsAg, HCV, HIV, VZV)	X																				
Serum pregnancy test[*2]	X																				
Urine pregnancy test[*2]		X			X				X		X		X	X	X	X	X	X	X	X	
Vital sign, weight, height[*3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigational Product Dispensing (or as needed)		X				X				X		X	X	X	X	X	X	X	X	X	X
Patient Dosing Diary review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination	X	X			X				X		X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessment																					
Hematology	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Clinical chemistry	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Urinalysis incl. sediment	X	X			X				X		X	X	X	X	X	X	X	X	X	X	X
Urine protein: creatinine ratio	X	X			X				X		X	X	X	X	X	X	X	X	X	X	X
Complement C3, C4,		X			X				X		X	X	X	X	X	X	X	X	X	X	X
ANA[*4] and anti-ds DNA Abs		X			X				X		X	X	X	X	X	X	X	X	X	X	X
ESR		X			X				X					X							X
Efficacy																					
CLASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Photography (selected)		X							X					X							
SLICC/ACR damage index		X																			X
SLEDAI-2K, MD Global Assessments, BILAG		X			X				X		X	X	X	X	X	X	X	X	X	X	X
Patient's Global Assessment, Skindex		X			X				X		X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic																					
Plasma TOFA-Part A (Cohort 1) [*5]		X[*6]																			
Pharmacodynamic																					
**Gene expression profiling of IL2 mediated genes in whole blood		X							X					X							
**Phosphospecific flow cytometry of blood T-cells & other relevant cells		X							X					X							
**SC-RNA SEQ in skin biopsies (selected)		X												X							
**Skin biopsy (selected) [*7]		X							X [*7]												
Safety																					
Adverse events/SAE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TT, diphtheria, varicella, influenza titer; EBV and CMV PCR	X													X							

[1*]**Part A - Day 5 after TD1**
[*2]**Females only**
[*3]**Height only at screening**
[*4]**ANA only at baseline on TD1**
[*5] **A total of 24.5 mL of blood will be taken at these visits for pharmacodynamics tests**
[*6]**PK samples will be drawn on Day 5 of Trial Week 1. re - morning dose for Day 5 and at 0.5, 1, 2, 4 and 8 hours post morning dose.**
[*7] **Two 3mm punch biopsies will be collected. 1st punch collected during week one. 2nd punch colleceted between weeks 8-15.**
****Assessment completed only at CCHMC**

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APPENDIX 1 Tofacitinib Experience in Juvenile Arthritis

ABSTRACT NUMBER: 388

Pharmacokinetics, Safety, and Tolerability of Tofacitinib in Pediatric Patients from Two to Less Than Eighteen Years of Age with Juvenile Idiopathic Arthritis

Hermine I. Brunner et al

Meeting: 2016 ACR/ARHP Annual Meeting

Date of first publication: September 28, 2016

Keywords: juvenile idiopathic arthritis (JIA), pharmacokinetics and tofacitinib

SESSION INFORMATION

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor that is being investigated for juvenile idiopathic arthritis (JIA). Here, we report the pharmacokinetics (PK), safety, and taste acceptability of tofacitinib following multiple oral doses in patients (pts) 2–<18 years (yrs.) old with active JIA.

Methods: Data were obtained from an open-label, non-randomized, multicenter, Phase I study (NCT01513902) where JIA pts were given 5 mg adult equivalent (based on body weight) of tofacitinib (tablet or solution) twice daily (BID) for 5 days (Table). There were 3 cohorts (COH) based on pt age, COH1: 12–<18 yrs, COH2: 6–<12 yrs, and COH3: 2–<6 yrs, with a target enrollment per group of ≥8 JIA pts for N=≥24 evaluable pts completing the study. Pts were enrolled in a stepwise approach beginning with the older age COH first. Subsequent younger age COH were enrolled following confirmation of safety and PK from the previous COH. PK parameters of tofacitinib were calculated using non-compartmental analysis of plasma concentration (conc)-time data. Taste acceptability of the solution formulation was listed and categorically summarized (frequency and %).

Results: 26 pts (COH1 [N=8], COH2 [N=9], and COH3 [N=9]) were included in this analysis. Pts' age ranged from 2–17 years; all were white except for one; there were 17 females and 9 males. Baseline disease characteristics were similar across all COH. All exposure metrics including geometric mean (GM) area under the conc-time curves (AUC), maximum (C), minimum (C) and predose (C) conc were lower in COH2 relative to those in COH1; however, due to higher doses in COH3 (modified after interim analysis of COH1 and 2), the mean AUC in COH3 was comparable to COH1. GM apparent volume of distribution (V /F) decreased with age (COH1=104.9 L, COH2=71.0 L, COH3=51.4 L). Average terminal half-lives (t) were COH1=2.62 h, COH2=1.95 h, and COH3=1.77 h. GM tofacitinib CL/F were 53%, 39%, and 11% higher in COH1, COH2, and COH3 pts, respectively, vs adult RA pts (18.4 L/h) receiving tofacitinib 5 mg BID. GM CL/F and V/F parameters were similar between males and females. Tofacitinib, administered over 5 days as multiple dose tablets or solution formulation, was well tolerated and taste for the solution formulation was found acceptable in children with active JIA. No serious adverse events or new safety signals were identified.

Conclusion: PK results from this study established dosing regimens for pts aged ≥2 years to be used in the upcoming efficacy and safety studies of tofacitinib in JIA pts. Tofacitinib was well tolerated in this study in JIA pts. Overall, pts found the taste of the tofacitinib solution formulation to be acceptable.

APPENDIX 2. Moderate or Potent CYP3A Inhibitors and Inducers

NOTE: Topical administration (e.g., cutaneous, ophthalmic, or intravaginal) of listed concomitant medications, which are prohibited if administered systemically, is allowed in the study.	
Moderate or Potent CYP3A Inhibitors	**Moderate or Potent CYP3A Inducers**
HIV antivirals:	efavirenz (Sustiva)
-delavirdine (Rescriptor)	nevirapine (Viramune)
-indinavir (Crixivan)	Barbiturates
-nelfinavir (Viracept)	carbamazepine (Carbatrol, Tegretol)
-ritonavir (Kaletra, Norvir)	modafinil (Provigil)
-saquinavir (Fortovase)	phenobarbital
-atazanavir	phenytoin (Dilantin, Phenytek)
amiodarone (Cordarone, Pacerone)*	rifabutin (Mycobutin)
cimetidine (Tagamet)	rifampin (Rifadin, Rifamate, Rifater)
clarithromycin (Biaxin, Prevpac)	rifapentine (Priftin)
telithromycin (Ketek)	St. John's Wort
clotrimazole	troglitazone (Rezulin)
chloramphenicol	**All Investigational Drugs**
diethyl-dithiocarbamate	**DMARDs**
diltiazem (Cardizem, Tiazac)	***All Biologics*****, such as: anakinra (Kineret), etanercept (Enbrel), adalimumab (Humira), infliximab (Remicade), abatacept (Orencia), canakinumab (Ilaris), tocilizumab (Actemra), golimumab (Simponi), rituximab (Rituxan),
erythromycin	
fluconazole (Diflucan)	
fluvoxamine (Luvox)	
Grapefruit juice and marmalade	
itraconazole (Sporanox)	
ketoconazole (Nizoral)	***Other DMARDs*****:** leflunomide, sulfasalazine, d-penicillamine, bucillamine, mizoribin, azathioprine, cyclosporine, tacrolimus, auranofin, aurothioglucose, aurothiomalate, staphylococcal protein A immuno-absorbant pheresis columns
mifepristone (Mifeprex, RU486)	
nefazodone (Serzone)	
norfloxacin (Shibroxin, Noroxin)	
mibefradil	
verapamil (Calan SR,Covera HS, Isoptin SR, Tarka, Verelan)	
voriconazole	

APPENDIX 3. Data Safety Monitoring Plan

DATA SAFETY MONITORING PLAN

Tofacitinib for Systemic Lupus Erythematosus With Cutaneous Lesions

(IND 132786)

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Since there are only 20 subjects, the PI will review all safety events that occur and no formal DSMB will be convened for this study.

A. SUMMARY OF THE PROTOCOL

This proposed study is an Investigator initiated clinical trial to study the safety and efficacy of *tofacitinib* (TOFA) for *systemic lupus erythematosus with cutaneous lesions* (SLE-CL). TOFA is approved under the brand name (XELJANZ) for the treatment of adult patients with moderate to severe rheumatoid arthritis (RA). Tofacitinib is also being developed for the treatment of psoriasis (oral and topical), Crohn's disease, ulcerative colitis, psoriatic arthritis, and ankylosing spondylitis and dry eye disease, and for the prevention of renal allograft rejection.

TOFA, a small molecule that inhibits Jak3, Jak1 and to a lesser degree Jak2, has been proven efficacious in RA in phase III trials. Notably, a series of Jak-STAT signalling cytokines, especially type I IFNs, IL-10 and IL-6, as well as the hormone prolactin, have been implicated in the pathogenesis of systemic lupus erythematosus (SLE). Such immunological abnormalities are thought to be even more pronounced among subjects with SLE onset early in life, i.e. with SLE diagnosis during childhood and adolescence (SLE). In this context, targeting the Jak-STAT pathway may be an attractive approach to manage inflammation and auto-immunity in SLE.

All type I IFN family members bind a common receptor complex (IFNAR1 and IFNAR2). Viral infection rapidly induces leukocyte production of IFN-a and -b, which initiates a JAK/STAT signaling cascade leading to transcription of target genes that promote host protection and viral elimination. IFN also promotes survival and differentiation of mature lymphocytes, class switching at immunoglobulin heavy chain loci, and activation of dendritic cells. The primary source of type I IFNs in the body is natural IFN-producing cells (NIPCs), also known as plasmacytoid dendritic cells (pDCs). Type I IFNs play a major role in the pathogenesis of SLE and have been shown to be associated with lupus-associated skin disease in murine studies

TOFA was efficacious in mouse models of skin inflammation induced by imiquimod application and IL-23 injection as assessed by clinical, histological and gene expression measures in the mouse ear. TOFA was also efficacious in a CD4+CD45RBhighCD25- T-cell transfer model that mimics aspects of psoriasis pathology and in a xenograft model where human psoriatic skin from psoriasis patients was transplanted onto severe combined immunodeficiency (SCID) mice. TOFA was efficacious in rodent and primate models of heterotopic heart transplantation and rodent models of arthritis by subcutaneous delivery in osmotic pumps (Changelian et al, 2003, Milici et al, 2008). Thus, TOFA shows promise in multiple models of autoimmunity and immune dysregulation.

Further, pDCs are actively recruited to inflammatory skin lesions of humans with SLE.

Additionally, blockage of interferon activity has been shown to ameliorate lupus skin disease.

To date, belimumab, hydroxychloroquine, chloroqine and quinacrine are approved for adults with *systemic lupus erythematosus (SLE)*. The latter three medications are approved also for cutaneous lupus without the system form of the disease, i.e. SLE. Despite these medications, chronic skin disease remains a major problem with SLE[7]. Given the severity of the disease, the unmet medical need, and the low number of available subjects in this specific population, it is judged acceptable to assess the safety, tolerability and PK as primary objectives; and efficacy as secondary objectives in an open-label manner.

B. BRIEF DESCRIPTION OF THE PROTOCOL (STUDY DESIGN)

This 76-week, 3-part, Phase 1b/2 study is intended to evaluate the pharmacological properties (pharmacokinetics and pharmacodynamics) of TOFA administrated to young adults with moderately to severely active inflammatory *SLE-CL*.

- **Part A** (up to week 8)requires stable background medications;
- **Part B** (up to week 24) allows for tapering of *corticosteroids (CS), in the setting of significant clinical improvement of SLE-CL as defined by a decrease in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI*) activity score by ≥50% from baseline *,* and

  Part C (until week 76) permits tapering of other background medications in subjects with clinical remission of SLE-CL (CLASI activity score=0). TOFA dosing is kept stable during Part C.

Primary Objective

Part A (Cohort 1):

- To evaluate the pharmacokinetic (PK) profiles of TOFA in young adults aged between 18 and including 45 years with SLE -CL who are on stable treatment for SLE

Part A (Cohort 1 and Cohort 2)

- To evaluate the safety and tolerability of TOFA in young adults with SLE -CL

Part B and C:

- To evaluate the safety and tolerability of TOFA in young adults with SLE -CL

Primary endpoints

Part A (Cohort 1 only):

- **Day 5:** AUC_{inf} and C_{max} of tofacitinib

Part B: At Week 24

- Nature, severity, and frequency of adverse events
- Incidence and severity of laboratory abnormalities

Key Secondary Objective(s) & Endpoint(s)

Secondary objectives

- To evaluate the efficacy of TOFA in young adults with SLE -CL

Secondary endpoint

Part A and B

Efficacy on SLE skin disease

- Proportion of subjects who achieve a skin response (complete or partial response) as per the validated Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) at weeks 4, 8 and 24 compared to baseline[16]. Response (compared to baseline at TD1) is defined as follows:
    - *Complete response (CR*) : complete resolution of the inflammatory rash (CLASI activity score = 0);
    - *Partial response (PR)*: ≥ 20% improvement of the CLASI activity score
    - *No response:* < 20% improvement or even worsening of the CLASI activity score (CLASI relapse)

Exploratory Objective(s) & Endpoint(s)

Exploratory objectives

Part A:

- To evaluate single cell expression patterns of skin biopsies of affected and non-affected skin with TOFA therapy
- To examine changes in interferon α/γ receptor, STAT phosphorylation patterns with TOFA therapy using immunohistochemistry
- To investigate mRNA expression patterns in peripheral blood upon treatment with TOFA with focus on interferon regulated genes

Parts B and C:

- To evaluate steroid sparing properties of TOFA for SLE -CL
- To evaluate TOFA effect of overall disease activity in SLE
- To evaluate effects of TOFA on quality of life

Exploratory endpoints at week 4, 8, 12, 24, 52, and 76

Part A:

- PD parameters include assessment of inhibitory effect of TOFA on expression of IL-2 responsive target genes downstream of the JAK/STAT pathway, such as FOXP3, SOCS3, IL-2Rα, interferon (IFN)-γ and granzyme B.

Parts B and C:

- Decrease of absolute dose of systemic CS from baseline
- Decrease of body weight adjusted CS dose from baseline

  - CS dosing is measured in prednisone-equivalents
- Proportion of subjects who discontinue systemic CS
- Proportion of subjects with cutaneous relapse
  - *Cutaneous relapse: a* new CLASI activity score ≥ 4 in those subjects who previously achieved CR of SLE -CL (CLASI = 0)
- Change of SLEDAI and BILAG score from baseline
- Absolute value and percent change in plasma: Complement C3, C4d, autoantibodies (anti-dsDNA)
- Change in number of inflamed joints from baseline[14]
- Change in SKINDEX score from baseline
- Change (increase) of CLASI damage score from baseline
- Change in the SLE core response variables (CRV) which include
  1. Change in SLEDAI score at each time point
  2. Change in protein: creatinine ratio at each time point.
  3. Change subject's overall well-being at each time point
  4. ESR
- Proportion of subjects with clinically important reduction in SLE activity at each time point, based on CRV changes compared to baseline
- Proportion of subjects with flare of SLE activity at each time point, based on CRV changes compared to baseline

Data of subjects who enter Part B before week 8 and/or Part C before week 24 will be considered on a last-observation (LOC) carried forward basis for endpoints of Part A and B, respectively.

C. INCLUSION/EXCLUSION CRITERIA

INCLUSION CRITERIA

1. Male or female age 18 to 45 years and >40 kg body weight.
2. Fulfills at least 4 out of the 11 Classification Criteria for SLE by the time of screening.
3. Written informed consent, given before any trial-related procedure. Subjects or their legal representative must have read and understood the informed consent form, must fully understand the requirements of the trial, and must be willing to comply with all trial visits and assessments.
4. CLASI activity score of 8 or higher at screening and baseline despite standard therapy.
5. Stable dose of prednisone of ≤ 20 mg/day within 2 weeks of enrollment.
6. Female subjects of childbearing potential must use a highly effective method of contraception to prevent pregnancy (abstinence is considered highly effective) and must agree to continue

to practice adequate contraception for the duration of their participation in the trial and for 28 days following the last dose of TOFA.

7. Female subjects of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at Trial Day 1 before dosing.
8. For subjects receiving leflunomide treatment, total daily dose does not exceed 20 mg.
9. A negative QuantiFERON-TB Gold In-Tube test performed within the 3 months prior to screening. A negative PPD test can be substituted for the QuantiFERON-TB.
10. Patients either have protective varicella titers or evidence of having been vaccinated against varicella.

EXCLUSION CRITERIA

Subjects are not eligible for this trial if they fulfill any of the following exclusion criteria:

1. Mild SLE -CL defined as a CLASI activity score of 7 or lower at screening and baseline
2. Increase in CS dosing within 2 weeks prior to Trial Day 1, or expected to require an increase in CS dosing during the first 4 weeks of the study.
3. Use of i.v. corticosteroids within4 weeks prior to Trial Day 1.
4. Increase in dosing of methotrexate, leflunomide, within 4 weeks before Trial Day 1 or expected to require an increase during the first 8-weeks of the study
5. Increase in dosing of hydroxychloroquine, or chloroquine within 4 weeks before Trial Day 1 or expected to require an increase during the first 8-weeks of the study
6. Rituximab within 1 year of Trial Day 1.
7. Increase in dosing of any medication or herbal treatment considered to have immunosuppressive properties within 4 weeks before Trial Day 1.
8. Prior treatment with or known intolerability of TOFA.
9. Use of cyclophosphamide (i.v. or oral), cyclosporine, or tacrolimus within 12 weeks prior to Trial Day 1.
10. Treatment with other investigational agents within the last 6 months or 5 half-lives, or as per washout requirement from the previous protocol, whichever is longer.
11. Estimated glomerular filtration rate (GFR) less than or equal to 60 mL/min per 1.73 m2
12. Known positive human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B surface antigen (HBsAg) serology.
13. Any condition, including findings in the laboratory tests, medical history, or other screening assessments, that, in the opinion of the Investigator, constitutes an inappropriate risk or a contraindication for participation in the trial or that could interfere with the trial's objectives, conduct, or evaluation.

14. Active central nervous system SLE deemed to be severe or progressive and/or associated with significant cognitive impairment leading to inability to provide informed consent and/or comply with the protocol.
15. Significant renal disease due to a reason(s) other than LN (e.g. diabetes mellitus, renovascular disease, or antiphospholipid syndrome).
16. Severely active Lupus Nephritis defined as a renal BILAG A score
17. History of dialysis within 3 months prior to Trial Day 1 or expected use during the trial duration.
18. History of or planned renal or other organ transplantation.
19. Known active clinically significant viral, bacterial or fungal infection, or any major episode of infection requiring hospitalization or treatment with parenteral anti-infectives within 8 weeks of screening, or completion of oral anti-infectives within 2 weeks before trial Day 1.
20. Breastfeeding or currently pregnant.
21. Legal incapacity or limited legal capacity to provide informed consent or assent.
22. Blood dyscrasias, including:
    - Hgb <10 g/dL or Hct <33%.
    - WBC <3.0 x 10^9/L.
    - Neutrophil count <1.2 x 10^9/L
    - Platelet count <100x 10^9/L.
    - Lymphocyte count of <0.5 x 10^9/L.
23. AST or ALT > 1.5 times the upper limit of normal or any other clinically significant laboratory abnormality.
24. History of any other rheumatic autoimmune disease.
25. Infections:
    - Latent or active TB or any history of previous TB.
    - Chronic infections.
    - Any infection requiring hospitalization, parenteral antimicrobial therapy or judged to be opportunistic by the investigator within the 6 months prior to the first dose of study drug.
    - Any treated infections within 2 weeks.
    - History of recurrent (more than one episode) herpes zoster or disseminated (a single episode) herpes zoster or disseminated (a single episode) herpes simplex.
    - History or current symptoms suggestive of any lymphoproliferative disorder, including Cytomegaly Virus (CMV) or Epstein Barr Virus (EBV) related lymphoproliferative disorder, history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease.
26. Patients taking potent and moderate cytochrome P450 3A4 (CYP3A4) inhibitors.

27. Patients taking potent and moderate CYP3A4 inducers.
28. Patients who have been vaccinated with live or attenuated vaccines within the 6 weeks prior to the first dose of study medication. All study participants should be up-to-date with respect to standard of care vaccinations (as defined by their country health ministry) as permitted by past immunosuppressive therapy for SLE.
29. Patients with a malignancy or with a history of malignancy with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.
30. Subjects with a history or current diagnosis of diverticulitis.

D. SAMPLE SIZE

This is a 3-part study designed to evaluate the PK-PD of TOFA in subjects 18-45 years with at least moderately active SLE -CL. Safety and efficacy will be evaluated as secondary objectives. No formal sample size estimation was done but previous TOFA studies in other populations suggest that 20 subjects are sufficient to achieve the objectives of this study.

It is planned to enroll:

Cohorts 1: n=10, weight > 40 kg and age $\geq$ 18 years up to and including age 45 years.

Cohort 2: n=10; weight > 40 kg and age $\geq$ 18 years up to and including age 45 years. Enrollment of subjects into Cohort 2 will commence once enrollment of Cohort 1 are completed and at least 1 subject in Cohort 1 showed at least partial improvement of SLE-CL. i.e. a 20% reduction of the CLASI activity score, between baseline and week 4.

E. TRIAL MANAGEMENT

For this study, all subjects will be recruited and followed at CCHMC and Metrohealth Medical Center.

It is planned to enroll:

Cohorts 1: n=10, weight > 40 kg and age $\geq$ 18 years and $\leq$ 45 years.

Cohort 2: n=10; n=10, weight > 40kg and age $\geq$ 18 years and $\leq$ 45 years .

Enrollment of subjects into Cohort 2 will commence enrollment of Cohort 1 are completed and at least 1 subject in Cohort 1 showed at least partial improvement of SLE-CL. i.e. a 20% reduction of the CLASI activity score, between baseline and week 4.

The general approach to evaluation is to enroll a total of 20 subjects aged 18 to 45 years with a body weight of > 40 kg. Besides population PK-sampling, Cohort 1 will undergo intense PK-evaluations during the Intense PK Period of Part A. Enrollment of subjects into Cohort 2 will commence once enrollment of Cohort 1 are completed and at least 1 subject in Cohort 1 showed at least partial improvement of SLE-CL. i.e. a 20% reduction of the CLASI activity score, between baseline and week 4. Subjects move from Part A to Part B to Part C of the study, unless they are discontinued from the study (see rescue clause Section 6.5 in the clinical protocol).

It is anticipated that almost all subjects are on stable background therapy with an antimalarial (hydroxychloroquine, rarely chloroquine), up to 80% are treated with corticosteroids (CS), and about 50% of the subjects will also be treated with a non-biological DMARD (mostly methotrexate, azathioprine and mycophenolate mofetil) for prior multiorgan involvement with SLE.

Based on TOFA PK in the RA population (body weight ranging from 40 kg-140 kg), clearance (CL) of TOFA is not dependent on body weight in adult subjects. Thus, the dose of TOFA in adults with body weight (BW) ≥40 kg was set to 5 mg twice daily (BID), an approved dose of TOFA in adult RA patients in most countries.

This clinical trial is the only one planned to be conducted this year under the IND. The trial will take 4 years.

F. TARGET POPULATION DISTRIBUTION (WOMEN, MINORITIES, ETC)

Twenty adult subjects diagnosed with SLE will be enrolled in this study. All subjects regardless of race and socioeconomic class will be considered potential study subjects.

This study follows procedures for minimizing risks and ensuring the safety and confidentiality of human subjects, as established under both the Department of Health and Human Services and the Office for Human Research Protections (OHRP). The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki and will be consistent with Good Clinical Practices (GCP) http://www.fda.gov/cder/guidance/959fnl.pdf and applicable regulatory requirements.

A common consent and assent form describing all aspects of the study will be used. Each participant and their legal guardian will be education about their risks and potential benefits. We will take appropriate measures to ensure the confidentiality of the data and the well-being of participants.

G. INSTITUTIONAL REVIEW BOARD PROTOCOL REVIEW

The protocol, informed consent, and assent will be reviewed and approved by the IRB.

Recruitment & Consent Procedures

The recruitment procedures for the trial will include a thorough explanation of the study, time commitments, possible risks and benefits, and alternative treatments. The patient must sign an informed consent forms that meets all current criteria of the FDA and local health regulations.

H. DATA SAFETY AND MONITORING PROCEDURES

All questionnaires and the results of the physical examination will be recorded on study forms. All forms will be assessed for completeness by the Clinical Research Coordinator. The Division of Rheumatology at Cincinnati Children's Hospital Medical Center will serve as study Coordinating Center.

ACTIONS TO ACHIEVE DATA SAFETY

All data will be entered into the Medidata Rave database on PCs in the Division of Rheumatology, CCHMC, stored and accessed in accordance with the HIPPA Standards [www.hhs.gov], HCFA's Internet Security Policy and other state and local requirements. The Medidata Rave database is maintained on servers by Medidata and back up is performed as outlined by medidata information security and privacy white paper. The Division of Biomedical Informatics at CCHMC distributes numerous computer packages for research purposes, including SAS [SAS Inc., Cary, North Carolina) and Microsoft software [see http://info.chmcc.org). Data monitoring of data collected at the CCHMC will be performed by the Division of Rheumatology research staff with assistance from the CCHMC *Office for Clinical and Translational Research* (OCTR).

MONITORING OF SITES

The PI will monitor the database of both CCHMC and Metrohealth Medical Center with assistance from CCHMC OCTR.

REPORTING OF ADVERSE EVENTS

Reporting of Adverse events will occur as part of the safety assessment of the study drug. We will use the National Cancer Institute (NCI) Common Toxicity Criteria, Version II for reporting.

All severe adverse events communicated to CC within one working day will be reported to the IRB within 2 working days. Based on the requirements for IND amendments outlined in the CFR §312.32, Dr. Brunner will be responsible for IND safety reporting including reporting of life-threatening and serious adverse events, unexpected adverse drug experience and the writing of the annual IND safety report.

CRITERIA FOR STUDY DISCONTINUATION

A subject will be considered a treatment failure and discontinued from the study if he/she experiences one or more of the following:

- Serious adverse event that is possibly related to TOFA;
- Important worsening of renal disease defined as a persistent increase in proteinuria as measured by the protein: creatinine (PC) ratio to values > 2.0 after achieving complete response, or doubling of proteinuria with values PC ratio >3.0 after achieving a partial response;
- Need to increase current or initiation of new SLE background therapy due to non-renal SLE;

- Life-threatening SLE complications as judged by the investigator;
- Need for more than the allowable CS rescue therapy as determined by the treating physician.
- No response of SLE-CL by Week 8

INTERIM ANALYSIS & SAFETY REVIEWS

No interim analyses are planned. The PI will continuously monitor the study for safety. An internal review of the study will be completed by CCHMC OCTR as outlined in the monitoring plan.

I. DATA MANAGEMENT

GENERAL INSTRUCTIONS FOR COMPLETING FORMS.

All data recorded on forms must be verifiable in the source documents maintained according to FDA and Good Clinical Practice (GCP) guidelines.

Subjects must not be identified by name on any study document submitted with the forms (i.e. lab reports). Replace subject names with subject initials and ID number.

Source documentation will comply with the following:

- **HEADER:** Complete the header information on every page, including pages for which no study data are recorded. Record subject's first, middle, and last initials (use a hyphen if no middle name). All dates must be verifiable by source documentation. Estimates are not acceptable.
- **ABBREVIATIONS:** Use of abbreviations not specifically noted in the instructions for completing the forms can be problematic and should be held to a minimum.
- **EXTRANEOUS WRITING:** Comments written extraneously on forms cannot be captured for monitoring and data analysis; thus, write only in the spaces indicated.
- **CORRECTING ERRORS:** If an error has been made on the study forms, place a **single** line through the erroneous entry and record the data and your initials. Indicate the correct response.
- **Do not leave forms incomplete or unused without explanation. Do not leave items blank without explanation**. Do not skip any items. Some items may carry "unknown" or "not applicable" response choices that should be checked when necessary. Incomplete forms that do not have adequate explanation compromise the integrity of the entire study.
- **INCOMPLETE DATA**: Errors, such as incomplete and illegible forms, are problems that require time and energy to resolve. Data may not be available to complete the form for various reasons. Circle the item for which data is not available and indicate the reason near the appropriate field:
    - If an evaluation was **not done,** write "ND" and provide a reason
    - If the information is **not available,** but the evaluation was done, write "NAV". Every effort should be made to obtain the information requested.

Only in rare circumstances, as in the case of lost documentation, should NAV be recorded on the form.

- If an evaluation is **not applicable**, write "NA".

- **INCOMPLETE FORMS:** If an entire page of the forms cannot be completed (all have no responses), and it is unlikely that it will be completed, draw a diagonal line through the form and write "NOT DONE, NOT AVAILABLE, or NOT APPLICABLE." The header information must be completed even though no data was recorded on the form.

RETENTION OF STUDY DOCUMENTATION

NIH policy requires that studies conducted under a grant retain participant forms for 3 years (7 years if under contract). Individual IRBs may have different requirements for record retention. FDA requires that informed consent forms be retained for 2 years after a marketing application is approved for a product or, if an application is not approved, until 2 years after shipment and delivery of the product is discontinued for investigational use and the FDA is notified. Investigators should retain forms for the longest applicable period.

SOURCE DOCUMENTATION

Patient data are collected on source documents [a paper case report form (CRF)]. Source documents are any documents on which study data are recorded for the first time. The PI must retain all study documents. The following are considered subject file documents:

- Case report forms
- Data correction forms (see QRF under Administrative Forms)
- Worksheets
- Source documents
- Signed subject consent/assent forms
- Hard copies of lab reports will be placed in the CRF binder kept on site. Lab data will be sent directly electronically to the Methodology Core for updating the database.

LOCUS OF COMPUTING

- The Data Management Center (DMC) at CCHMC will design and manage the Medidata Rave database.
- The DMC at CCHMC will program the database with integrated query management. Data can be queried based on field settings, programmed logical checks, and manual checks.
- An audit trial will be maintained on all data entry. All changes made to a data point are tracked by the audit trail. The audit trail is viewable based on role permissions. Information collected in the audit trail includes: action, user name and ID, and date /time performed. A more detailed audit trail report can be generated by DMC as required.

DATA ENTRY

Only properly trained persons directly involved with the study protocol will begranted access. The DMC will invite users to the study with the appropriate role and site assignment. Users must create an iMedidata account. The iMedidata account is owned and controlled by the individual. The DMC requires role specific online Rave training before gaining access to the study database.

Double data entry will not be used for this study. Edit procedures are in place during data entry.

HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT (HIPAA)

Medidata Rave complies with Health Insurance Portability and Accountability Act of 1996 (HIPPA) guidelines, by storing all data in protected areas, assigns all users roles that control data access and read/write privileges and tracks any changes. Moreover, IRB approval and patient consent is required before any data can be entered.

MEDIDATA RAVE AUDIT TRAIL:

- **Creation of data:** The data can only be entered by authorized personnel. These individuals must log onto the system with their iMedidata account username and individually selected password. Individuals should log off the system after each session to prevent unauthorized entries.

- **Modification of data:** Data modification can only be done by authorized personnel. Reasons for changes to the data will be collected. Individuals should log off after each session to prevent unauthorized entries**Deletion** of data: Deletion of data can only be done by authorized personnel. However, subjects, forms, and log lines cannot be truly deleted. A request would need to be made to the DMC to inactivate an entire subject. The subject will be made inactive and inaccessible in EDC and will not be a part of data exports. Similarly, log lines and individual forms may also be made inactive. Users with data entry privileges are able to inactivate log lines and forms. The data will still be viewable in EDC, but will not be a part of the data export. All inactive data can be reactivated as appropriate.An **audit trail** is recorded. The audit trail includes information on: action, user name and ID, and date/time performed.

J. DATA ANALYSIS PLAN

Pharmacokinetic/dynamic analysis will occur on de-identified data by PFIZER. In brief, NONMEM modeling will be done and exposures to TOFA analyzed under consideration of patient weight and concomitant medications (steroids yes/no). All other analyses will be done by a trained biostatistician working at CCHMC .

See details in Protocol Section 8, Planned Statistical Analyses.

Categorical outcomes parameters will be summarized in frequencies/ rates and numeric outcomes will be assessed using paired t-tests. In analyses that adjust for concomitant medications, ANOVA will be done and least-square means calculated.

Frequencies of adverse events by seriousness will be summarized per MEDDRA lower level term and/or NCI Common Toxicity Criteria lower-level term.

K. REGULATORY ISSUES

ADVERSE EVENT REPORTING DEFINITIONS

Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage.

Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Requires or Prolongs Hospitalization: Hospital admissions scheduled prior to the study, are not considered serious adverse events unless the hospitalization is prolonged due to an adverse event. Planned admissions as part of a study, hospitalizations for scheduled treatment of a pre-existing condition that has not worsened, and hospitalization for an elective procedure are not considered serious adverse events.

AE/SAE DATA COLLECTION AND REPORTING

Adverse Event Data Collection and Reporting Procedures. During a clinical trial, the reporting of adverse experience information can lead to important changes in the way a new treatment is developed, as well as provide integral safety data. All AEs will be reported on the AE pages of the CRF. All serious adverse events that occur, regardless of causality, will require immediate reporting (within 24 hours of knowledge to Pfizer. For any adverse event meeting the definition of fatal or "life threatening," the investigator will notify Pfizer immediately. The IRB will be notified per IRB policy of SAE/AE that is both related to study drug and unexpected. All other AEs not fitting related/unexpected criteria will be reported to per IRB policy. Subjects or subjects' partners who become pregnant during subject's TOFA treatment will be reported on an SAE form with the addition of an *Exposure in Utero* (EIU) Supplemental Form, regardless of whether an SAE has occurred. Pregnancy SAE and EIU form will be submitted to Pfizer within 24 hours of awareness of the exposure and to the IRB per IRB policy.

See Protocol Section 7.7 Safety & Adverse Event Reporting for additional information.

WOMEN OF CHILDBEARING POTENTIAL

Patients must not be and should not become pregnant during exposure to study drug. Sexually active female participants must use an effective method of birth control during the study. The informed consent form will indicate that the investigator has reviewed information about pregnancy prevention for all women of childbearing potential. A serum or urine β-HCG will be performed at randomization. Pregnancy testing will be repeated throughout the study as deemed necessary by the treating physician.

L. *RISKS & BENEFITS*

1. RISKS

- **Privacy and confidentiality risks:** All study results will be kept confidential. All patient identifiers will be removed prior to data transmission to the CC at CCHMC. The study and study information will follow regulations of the Good Clinical Practice Guidelines.
- **Financial risks:** Patients will not be charged for the study procedures and study blood draws. The patient's insurance company will be charged for continuing medical care and/or hospitalization including tests and treatments of any side effects of tofacitinib. In the event that the patient insurance does not cover cost, the patient may incur additional costs because of treatment side effects.
- **Blood draws** may cause discomfort when the needle passes through the skin and may cause bruises and even infections. The study personnel will attempt to combine study blood draws with those necessary for all subjects.

The following **side-effects** are associated with Tofacitinib:

- **Very common side effects** (≥10%): upper respiratory tract infection (nasopharyngitis, common cold).
- **Common side effects** (≤ 10%): lung infection (pneumonia and bronchitis), shingles (herpes zoster), influenza (flu), sinusitis, urinary bladder infection (cystitis), sore throat (pharyngitis), viral infections affecting the gut, increased liver enzymes, muscle enzymes or cholesterol, weight gain, stomach (belly) pain (which may be from inflammation of the stomach lining), vomiting, diarrhoea, nausea, indigestion, pain in the muscles and joints, low white blood cell count, low red blood cell count (anaemia), fever, fatigue (tiredness), swelling of the feet and hands, headache, high blood pressure (hypertension), poor sleep, shortness of breath or difficulty breathing, cough, rash, itching.
- **Uncommon side effects** (1%): blood infection (sepsis), tuberculosis, kidney infection, skin infection, herpes simplex or cold sores (oral herpes), blood creatinine increased (a possible sign of decreased kidney function), dehydration, muscle strain, tendonitis, joint swelling, joint infection, ligament sprain, abnormal sensations, sinus congestion, skin redness, fatty liver, inflammation of outpouchings of the intestine (diverticulitis), tears in the stomach or intestines, viral infections, some types of skin cancers (nonmelanoma-types).
- **Rare side effects** (0.1%): tuberculosis involving the brain and spinal cord, bones and other organs, and other unusual infections.

- **Serious infections**
- Tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that can spread throughout the body. Some people have died from these infections.
- Viral reactivation, including herpes zoster, in Asian people may be higher than for non-Asian people. This higher risk has been seen in people with rheumatoid arthritis and psoriasis who have been treated with tofacitinib.
- **Cancer and immune system problems**
- Skin cancers, lymphoma and other cancers including lung, breast, melanoma, prostate and pancreatic cancer.
- Some people who have taken oral tofacitinib with certain other medicines to prevent kidney transplant rejection have had a problem with certain white blood cells growing out of control (Epstein Barr Virus-associated post transplant lymphoproliferative disorder).
- **Tears or holes (perforation) in the stomach or intestines**
- Gastrointestinal perforation has been observed in clinical trials in patients with rheumatoid arthritis.
- **Changes in certain laboratory test results**
- Changes in lymphocytes, neutrophils counts, hemoglobin, liver enzymes and lipids.

Based upon the information provided above, the risks associated with the study are rated to be low to moderate.

ACTIONS TAKEN TO MINIMIZE RISKS

This study follows procedures for minimizing risks and ensuring the safety and confidentiality of human subjects, as established under both the Department of Health and Human Services and the Office for Human Research Protections (OHRP). The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki and will be consistent with **Good Clinical Practices (GCP) http://www.fda.gov/cder/guidance/959fnl.pdf** and applicable regulatory requirements.

To mitigate these risk, we plan to:

- Exclude participants who may be at an increased risk for these side effects
- Prohibit the use of immunizations using live vaccines during study participation
- Prohibit the use of medications with known drug interactions with tofacitinib
- Conduct subject monitoring during the course of the study to assess safety of participants, including laboratory monitoring.
- Con-medication monitoring for potential drug interactions
- Conduct follow up safety visits and discontinuation of treatment
- **Reporting of Adverse Events:** Reporting of Adverse events will occur as part of the safety assessment of the study drug. We will use the National Cancer Institute (NCI) Common

Toxicity Criteria, Version II for reporting. All severe adverse events communicated to CC within 48 hours and reported to the IRB within 2 working days.

- **Based on the requirements for IND amendments outlined in the CFR §312.32, Dr. Brunner will be responsible for IND safety reporting including reporting of life-threatening and serious adverse events, unexpected adverse drug experience and the writing of the annual IND safety report.**

2. BENEFITS

Subjects may or may not receive benefit from this study.

M. PREMATURE CLOSURE OF STUDY

CRITERIA FOR STUDY DISCONTINUATION

A subject will be considered a treatment failure and discontinued from the study if he/she experiences one or more of the following:

- Serious adverse event that is possibly related to TOFA;
- Important worsening of renal disease defined as a persistent increase in proteinuria as measured by the protein: creatinine (PC) ratio to values > 2.0 after achieving complete response, or doubling of proteinuria with values PC ratio >3.0 after achieving a partial response;
- Need to increase current or initiation of new SLE background therapy due to non-renal SLE;
- Life-threatening SLE complications as judged by the investigator;
- Need for more than the allowable CS rescue therapy as determined by the treating physician.

N. TRIAL EFFICACY

No interim analysis is planned to assess efficacy of tofacitinib.

APPENDIX 4

The Skindex-29 Dermatology Survey of Quality of Life (Patient)

These questions concern your feelings about the skin condition that has bothered you the most.
How often during the past FOUR weeks do these statements describe you?
Check the answer that comes closest to the way you have been feeling.

	Never 1	Rarely 2	Sometimes 3	Often 4	All the time 5
1. My skin hurts	☐	☐	☐	☐	☐
2. My skin condition affects how well I sleep	☐	☐	☐	☐	☐
3. I worry that my skin condition may be serious	☐	☐	☐	☐	☐
4. My skin condition makes it hard to work or do hobbies	☐	☐	☐	☐	☐
5. My skin condition affects my social life	☐	☐	☐	☐	☐
6. My skin condition makes me feel depressed	☐	☐	☐	☐	☐
7. My skin condition burns or stings	☐	☐	☐	☐	☐
8. I tend to stay at home because of my skin condition	☐	☐	☐	☐	☐
9. I worry about getting scars from my skin condition	☐	☐	☐	☐	☐
10. My skin itches	☐	☐	☐	☐	☐
11. My skin condition affects how close I can be with those I love	☐	☐	☐	☐	☐
12. I am ashamed of my skin condition	☐	☐	☐	☐	☐
13. I worry that my skin condition may get worse	☐	☐	☐	☐	☐
14. I tend to do things by myself because of my skin condition	☐	☐	☐	☐	☐
15. I am angry about my skin condition	☐	☐	☐	☐	☐
16. Water bothers my skin condition (bathing, washing hands)	☐	☐	☐	☐	☐
17. My skin condition makes showing affection difficult	☐	☐	☐	☐	☐
18. I worry about side effects from skin medications/treatments	☐	☐	☐	☐	☐
19. My skin is irritated	☐	☐	☐	☐	☐
20. My skin condition affects my interactions with others	☐	☐	☐	☐	☐
21. I am embarrassed by my skin condition	☐	☐	☐	☐	☐
22. My skin condition is a problem for the people I love	☐	☐	☐	☐	☐
23. I am frustrated by my skin condition	☐	☐	☐	☐	☐
24. My skin is sensitive	☐	☐	☐	☐	☐
25. My skin condition affects my desire to be with people	☐	☐	☐	☐	☐
26. I am humiliated by my skin condition	☐	☐	☐	☐	☐
27. My skin condition bleeds	☐	☐	☐	☐	☐
28. I am annoyed by my skin condition	☐	☐	☐	☐	☐
29. My skin condition interferes with my sex life	☐	☐	☐	☐	☐
30. My skin condition makes me tired	☐	☐	☐	☐	☐

APPENDIX 5

Cutaneous LE Disease Area and Severity Index (CLASI)

Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion

	activity		damage		
Anatomical Location	Erythema	Scale/ Hypertrophy	Dyspigmentation	Scarring/ Atrophy/ Panniculitis	Anatomical Location
	0-absent 1-pink; faint erythema 2- red; 3-dark red; purple/violaceous/ crusted/ hemorrhagic	0-absent; 1-scale 2-verrucous/ hypertrophic	0-absent, 1-dyspigmentaton	0 – absent 1 – scarring 2 – severely atrophic scarring or panniculitis	
Scalp				See below	Scalp
Ears					Ears
Nose (incl. malar area)					Nose (incl. malar area)
Rest of the face					Rest of the face
V-area neck (frontal)					V-area neck (frontal)
Post. Neck &/or shoulders					Post. Neck &/or shoulders
Chest					Chest
Abdomen					Abdomen
Back, buttocks					Back, buttocks
Arms					Arms
Hands					Hands
Legs					Legs
Feet					Feet

Mucous membrane

Mucous membrane lesions (examine if patient confirms involvement)	
0-absent; 1-lesion or ulceration	

Dyspigmentation

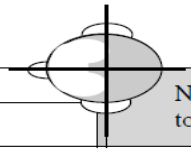
Report duration of dyspigmentation after active lesions have resolved (verbal report by patient – tick appropriate box)

☐ Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains)

☐ Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

Alopecia

Recent Hair loss (within the last 30 days / as reported by patient)	
1-Yes 0-No	



NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both

Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.

Alopecia (clinically not obviously scarred)		Scarring of the scalp (judged clinically)	
0-absent 1-diffuse; non-inflammatory 2-focal or patchy in one quadrant; 3-focal or patchy in more than one quadrant		0- absent 3- in one quadrant 4- two quadrants 5- three quadrants 6- affects the whole skull	

Total Activity Score
(For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia)

Total Damage Score
(For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp)