Abbreviated Title: Tofacitinib in Sjögren's syndrome

NIH IRB #: 20D0131

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Title: Safety of Tofacitinib, an oral Janus Kinase Inhibitor, in primary Sjögren's syndrome Phase Ib-IIa placebo-controlled clinical trial and associated mechanistic studies

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Investigational Agents:

Drug Name:	Tofacitinib
IND Number:	Exempt
Sponsor:	NIDCR
Manufacturer:	Pfizer

TABLE OF CONTENTS

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1.1 SYNOPSIS

Title: Safety of Tofacitinib, an oral Janus kinase (JAK) inhibitor, in primary Sjögren's syndrome (SS); a Phase Ib-IIa placebo controlled clinical trial and associated mechanistic studies

Study Description: As a primary objective, this study represents an innovative investigative measure of the safety and tolerability of JAK inhibition in participants with primary Sjögren's syndrome. Secondary objectives will include investigating the effects of Tofacitinib on target tissues (e.g., salivary glands), systemic inflammation, and on vascular function in SS participants. We also aim to identify biomarkers of response that may be useful as endpoints in future studies.

Objectives:

Primary Objective:

- To determine the safety and tolerability of Tofacitinib in participants with SS and mild to moderate disease activity.

Secondary Objectives:

- To assess clinical improvement after treatment with Tofacitinib as measured by changes in the European League Against Rheumatism (EULAR) Sjögren's syndrome Disease Activity Index (ESSDAI) and no worsening on the Physician's Global assessment Scale (PGA).
- To demonstrate that treatment with Tofacitinib is effective clinically and biologically in SS individuals with mild to moderate disease.
- To investigate the effects of Tofacitinib on systemic biomarkers of SS as measures biological effects that can be used as outcome measures to power a larger Clinical Trial.

Endpoints:

Primary Endpoint:

- Safety and tolerability will be measured by assessment of adverse events (AEs) and clinical safety laboratory tests throughout the study. Toxicity is defined as any study drug-related Grade 3 adverse event or higher (as measured by the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0).

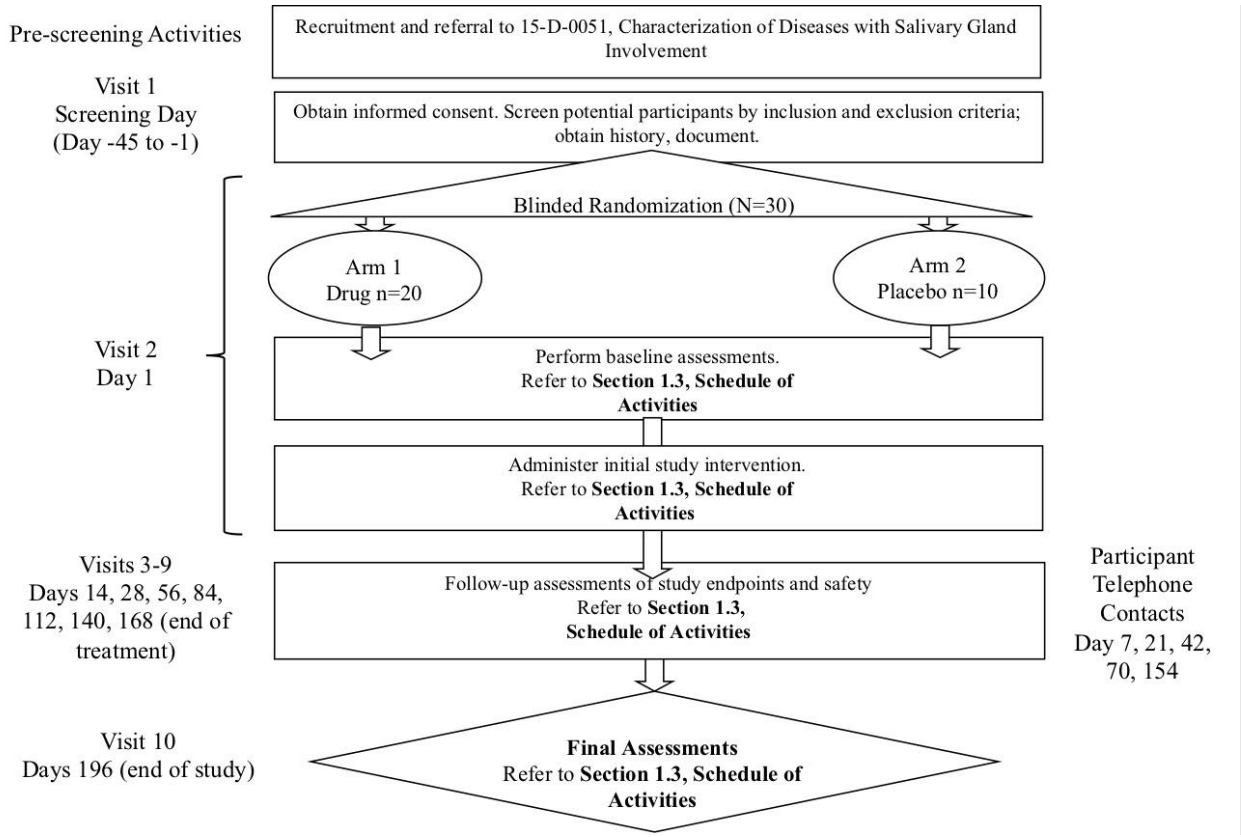
Secondary Endpoints:

Preliminary assessments of clinical response will be measured by:

- Changes in the ESSDAI score between Baseline and Day 168 (end of treatment)

	• Changes in the Physician's Global Assessment (PGA) scores between baseline and study day 168.
Study Population:	Adult patients with Primary Sjögren's syndrome of mild to moderate disease activity
Phase:	Ib-IIa randomized, double blind, placebo controlled clinical trial
Description of Sites/Facilities Enrolling Participants:	Single-site study to be conducted at NIH Clinical Research Center (CRC)
Description of Study Intervention:	Administration of oral Tofacitinib, 5 mg twice daily, for the treatment of SS participants with mild to moderate disease activity.
Study Duration:	Start Date: 09/20/2020 End Date: 09/20/2024 (Four (4) years)
Participant Duration:	A maximum of 241+/-45 Days

1.2 SCHEMA


Pre-screening Activities
Recruitment and referral to 15-D-0051, Characterization of Diseases with Salivary Gland Involvement
Visit 1
Screening Day
(Day -45 to -1)
Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document.
Blinded Randomization (N=30)
Arm 1
Drug n=20
Arm 2
Placebo n=10
Visit 2
Day 1
Perform baseline assessments.
Refer to Section 1.3, Schedule of Activities
Administer initial study intervention.
Refer to Section 1.3, Schedule of Activities
Visits 3-9
Days 14, 28, 56, 84, 112, 140, 168 (end of treatment)
Follow-up assessments of study endpoints and safety
Refer to Section 1.3, Schedule of Activities
Participant Telephone Contacts
Day 7, 21, 42, 70, 154
Visit 10
Days 196 (end of study)
Final Assessments
Refer to Section 1.3, Schedule of Activities

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	SCR – Visit 1 -45 days to Day 1*	Baseline Visit 2 D 1	D7 t/call (+/- 3 days)	Visit 3 D 14	D21 t/call (+/- 3 days)	Visit 4 D 28	D42 t/call(+/- 3 days)	Visit 5 D 56	D70 t/call(+/- 3 days)	Visit 6 D 84	Visit 7 D 112	Visit 8D 140	D154 t/call (+/- 3 days)	End ofTx. Visit 9 D 168	End of Study Visit 10 D 196	UNSCH visit: AE or other reason
Informed Consent	X															
Review of inclusion and exclusion criteria	X															
Vital sign measurements	X	X		X		X		X		X	X	X		X	X	X
Dental History and Oral and Head and Neck Exam	X	X								X				X	X	
Saliva Collection	X	X								X				X	X	
Salivary Flow Rate	x	X								X				X	X	
Oral Microbiome/ Plaque Collection		X												X		
Salivary Gland Ultrasound	X									X				X		
Comprehensive Ophthalmic Examination, Schirmer's test	X (with fundoscopy and MMP-9)									X				X (with MMP-9)	X	
EKG	X	X												X	X	X
Concomitant medications review.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Minor Salivary Gland Biopsy	X													X		
Presenting Symptoms-Abbreviated Medical History and physical examination	X	X		X		X		X		X	X	X		X	X	X
Complete blood count with differential	X	X		X		X		X		X	X	X		X	X	X
Blood/serum chemistries: (creatinine, glucose, urea nitrogen, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, albumin)	X	X		X		X		X		X	X	X		X	X	X
Pregnancy test (serum or urine; for females with reproductive potential only)	X	X		X		X		X		X	X	X		X	X	X
Urinalysis and Random urine Protein/Creatinine ratio	X	X		X		X		X		X	X	X		X	X	X
BK virus quantitative PCR-urine and blood	X	X		X		X		X		X	X	X		X	X	X
Lipid Panel low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG) and total cholesterol(TC)	X	X								X				X	X	X
Lipoprotein Profile (Apolipoprotein A-1 Apolipoprotein	X	X								X				X	X	X
Lymphocyte pheno-TBNK		X								X				X	X	X
Inflammatory Markers (hs-CRP, ESR)		X				X		X		X	X	X		X	X	X

Procedures	SCR Visit 1 -45 days to Day 1	Baseline Visit 2 D 1	D7 t/call (+/- 3 days)	Visit 3 D 14	D21 t/call (+/- 3 days)	Visit 4 D 28	D42 t/call (+/- days)	Visit 5 D 56	D70 t/call (+/- 3 days)	Visit 6 D 84	Visit 7 D112	Visit 8 D 140	D154 t/call (+/- 3 days)	End of Tx. Visit 9 D168	End of Study Visit 10 D196	UNSCH visit: AE or other reason
Serologies: antinuclear antibodies, anti-ENA panel (anti-RNP, anti-SmRNP, anti-SSA, anti-SSB) anti- dsDNA antibodies, anticardiolipin antibodies, lupus anticoagulant, anti-beta2-glycoprotein antibodies,	X	X								X				X	X	X
C3 complement, C4 complement	X	X				X		X		X	X	X		X	X	X
Quantitative immunoglobulin IgA, IgG and IgM	X	X				X		X		X	X	X		X	X	X
Varicella IgG-(antibody)	**x**															
Screening serologies for hepatitis B, hepatitis C and HIV	X															
Screening Tuberculosis using the Quantiferon Gold test	X															
Anti-SARS-CoV-2 antibodies		X												X		
Research labs		X								X				X	X	X
Cryoglobulins	X															
Serum protein electrophoresis (SPEP)	X									X				X	X	X
Randomization		X														
Study Drug Administration D1- D168, Dose BID. 1st dose at NIH on D1		X				X		X		X	X	X		X		X
Drug Accountability		X	X	X	X	X	X	X	X	X	X	X	X	X		X
Adverse event review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of biologic effect(s)		**X**								**X**				X	X	
Assessment of durability of the clinical and biologic effects.										**X**				X	X	
Mechanistic studies: (intracellular signaling molecules, cytokine expression, circulating immune cell types and autoreactive B cells.) All samples can be run simultaneously for each assay at the end of the study		**X**								**X**				X	X	
Patient questionnaires 1. SF-36 2. FSS 3. PROMIS 4. Dry Mouth Questionnaire 5. Xerostomia VAS 6. OHIP-14 7. AECG symptom Questionnaire		X								X				X	X	X

8. ESSPRI																
Assessment of SS disease activity **1. ESSDAI** **2. Physician Global Assessment (PGA)**	X	X				X		X		X	X	X		X	X	X
Vascular Function Studies (SphygmoCOR, CAV1 and Endopat)		X								X				X	X	
All study efficacy dates are ±7 days * Screening labs may be used if completed on prior protocols within 30 days of Screening Day.																

2 INTRODUCTION

2.1 STUDY RATIONALE

The proposed research is a Phase Ib-IIa clinical trial, whose primary focus is to test the safety of Tofacitinib, a JAK inhibitor, in mild to moderate SS. A secondary goal is to perform exploratory mechanistic studies as a prologue to future studies in SS and to identify candidate surrogate markers that might relate to or predict clinical efficacy of JAK inhibition within this population. This clinical trial seeks to address an unmet clinical need: SS is a chronic systemic autoimmune disease of unknown etiology, with no cure, and current therapeutic strategies are limited in their efficacy.

2.2 BACKGROUND

Primary Sjögren's syndrome (SS) is an autoimmune disease with heterogeneous clinical presentation resulting from involvement of multiple biologic pathways. The pathways that lead to loss of tolerance in SS include: multiple autoreactive cell types (B, T, dendritic, Th17 and regulatory T cells), abnormal cytokine milieus, genetic factors, and environmental and hormonal influences, all of which can influence cell differentiation patterns and reset tolerance checkpoints (Glauzy et al., 2017).

Tofacitinib is an orally administered JAK inhibitor that has been approved by the Food and Drug Administration for the treatment of moderate to severe rheumatoid arthritis (RA), psoriatic arthritis (PsA), and moderate to severe ulcerative colitis (UC).

The JAKs are a family of intracellular enzymes (JAK1, 2 and 3 and TYK2) that mediate signaling through a broad range of cytokine receptors via the signal transducer and activator of transcription proteins (STATs) [1,2]. Targeting JAKs is an attractive therapeutic possibility for SS for many reasons. Many of the inflammatory cytokines implicated in the pathogenesis of SS signal via the JAK-STAT pathways. JAK inhibitors have been found to have efficacy in various murine models of SS. A mouse model of SS treated with a JAK inhibitor exhibited improvement in salivary flow rates and suppression of lymphocyte infiltration in salivary glands.

2.2.1 Sjögren's Syndrome; description and epidemiology

Sjögren's syndrome is a systemic autoimmune disease with heterogeneous clinical presentation. The disease primarily affects females and is manifested by chronic inflammatory lymphocytic infiltration of the exocrine glands leading to their dysfunction and ultimate destruction of the tissue. This autoimmune exocrinopathy may occur alone (primary Sjögren's syndrome) or may coexist with other systemic connective tissue disorders (secondary Sjögren's syndrome). Salivary and lacrimal glands are predominantly affected leading to xerostomia (dry mouth) and xerophthalmia (dry eyes) although other exocrine gland tissues may be affected including: the skin (cutaneous xerosis); the upper respiratory tract causing epistaxis, hoarseness and bronchial hyper-responsiveness; and the vagina (vaginal xerosis) that increases the rate of vaginal infections and dyspareunia.

Participants may experience painful recurrent parotid swelling, profound fatigue, widespread musculoskeletal pain, and polyarthritis. Patients with SS experience 5-fold higher rates of lymphoma than the general population and an 8-fold increased lymphoma- associated risk of mortality.

The prevalence of SS is estimated at 0.5 – 4%, making it one of the most prevalent autoimmune diseases[1]. SS occurs throughout the world and susceptibility is clearly modulated by ethnicity and gender1. Although it affects both males and females of all age groups, it most commonly affects middle-aged women, typically in the fourth to sixth decades of life, with a striking female predilection of approximately 9:1.

While a precise etiology of SS remains unknown, the pathogenesis is thought to be multifactorial including an environmental trigger (i.e., viral) in a genetically predisposed individual. The subsequent immune response, involving innate and adaptive immunity, leading to the development of autoimmunity and chronic inflammation, are central components of the disease process[2]. Even though concordance in monozygotic twins has not been established, familial and monozygotic twins with SS have been reported. For the vast majority of individuals with SS the genetic contribution appears to be polygenetic[3]. Despite rigorous genome wide association studies, only a handful of candidate risk loci have been detected and all have been in non-coding regions of the genome[3]. Additionally, non-genetic contributors to disease factors (i.e., hormonal and environmental factors) also seem to be important in the pathogenesis of disease. Therefore, complex gene-environment interactions driving this disease have not yet been deciphered.

2.2.2 Current Treatment Paradigms in SS

The current management of individuals with SS is usually stratified by the degree of internal organ involvement; however, most treatment strategies include a variety of immunosuppressive medications that are limited in their efficacy and local and systemic approaches to mitigate symptoms (e.g., treatment of dry eyes and dry mouth)[4].

Treatment of dry mouth

The treatment of oral dryness is largely symptomatic[4]. Artificial saliva preparations (e.g. Saliva replacement) are available; the mainstay of replacement therapy consists of frequent sips of water or other sugar-free fluids, which are poorly effective. Various fluoride applications including prescription-strength toothpaste, fluoride gels and oral rinses are used to prevent dental decay. Oral candidiasis, a common consequence of salivary dysfunction and dry mouth related

dysbiosis is treated with topical or systemic anti-fungal medications such as nystatin rinse or systemic fluconazole.

If dry mouth is not adequately controlled with replacement methods, pharmacological therapy with sialagogue drugs is an option [5]. Two drugs are approved for this indication: pilocarpine (5 mg three times a day) and cevimeline (30-60 mg three times a day). Both act on muscarinic receptors and increase exocrine gland secretion.

However, acceptance and efficacy of muscarinic agonists is only moderate due to unacceptability of side effects, including sweating, vision changes, nausea, and flushing.

Treatment of dry eyes

Many tear substitutes are available and are commonly used by affected individuals to alleviate ocular dryness. Preservative free preparations are preferred especially if used more than four times a day. Cyclosporine ophthalmic solution (0.05%, 1 drop every 12 hours) has been approved for the treatment of keratoconjunctivitis sicca.

A frequently used surgical option is the occlusion of the puncta to block tear drainage and consequently increase moisture. Pilocarpine and cevimeline can be effective for dry eyes, too, especially in individuals with the most severe dryness[5].

Treatment of extra-glandular manifestations

The treatment of musculoskeletal manifestations of SS is similar to those of other systemic rheumatologic diseases[6]. Antimalarial drugs, such as hydroxychloroquine, are effective for arthralgia/arthritis, myalgia and fatigue[7]. Visceral and neurologic manifestations are treated with corticosteroids and immunosuppressive drugs.

Several randomized case-control studies focused on therapy for SS using biologic agents, such as the tumor necrosis factor (TNF) blocking agents, infliximab[8] and etanercept[9], but none of the studies exhibited clinical benefit.

Treatment of lymphoma in Sjögren’s syndrome is the same as in the general population6. Most Sjögren’s syndrome-associated lymphomas are low-grade B cell lymphomas localized in the exocrine glands. For these, watchful waiting may be the most appropriate treatment option. Higher grade lymphomas require more aggressive treatment with cytotoxic regimen and/or radiation therapy.

Disease pathogenesis; cytokines in Sjögren's syndrome.

The pathogenesis of SS appears to involve the complex interaction of genetic, environmental, and hormonal factors. Activation of several biological pathways belonging to both innate and acquired immune systems such as Type I and II interferons (IFN)[10-12], aberrant T-regulatory activity[13], augmented function of helper T-cells[14], lymphoneogenesis with germinal center formation[15], and abnormal B-cell activation with clonal expansion[16] have been reported. Epithelial damage, due to pathogen, genetic predisposition, or idiopathic insult, and altered immune responses may result in apoptosis of salivary (or other target organs) epithelial cells and could be responsible for relocalization and release of autoantigens[17].

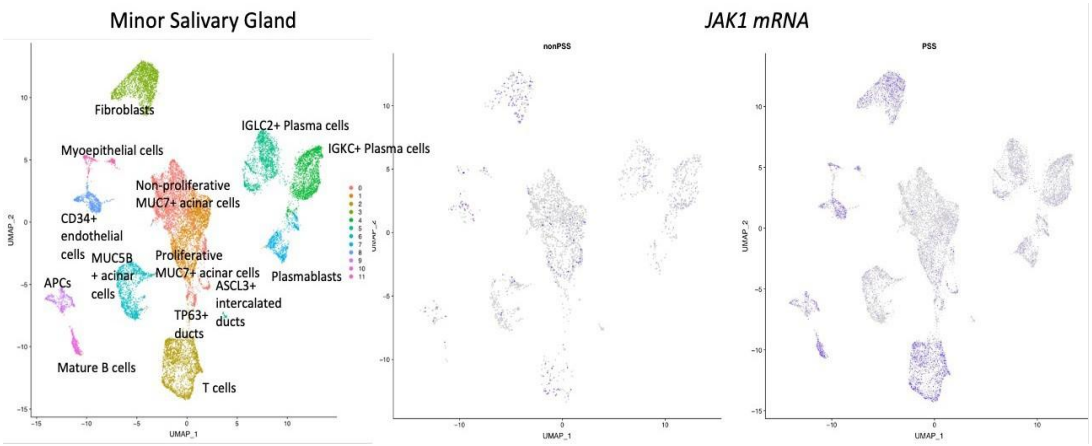


Figure 1. Annotated UMAP single cell atlas of the minor salivary glands and JAK1 mRNA expression in minor salivary gland cells.

These autoantigens result in stimulation of intrinsic cellular responses with engagement of toll-like receptors (TLRs), e.g. TLR3 in epithelial cells, and TLR7 and

TLR8 in plasmacytoid dendritic cells (pDCs), resulting in local up-regulation of Type I IFNs and IL-12[18,19]. Increases in Type I IFNs induces release of B-cell activating factor (BAFF) stimulating B-cell activation, [20] autoantibody production and eventual formation of immune complexes that can stimulate pDCs enhanced release of Type I IFN[21].

Interleukin (IL)-12, along with Type I IFNs, stimulates both natural killer cells (innate) and Th1 cells (adaptive), increasing IFNγ (Type II IFN) production mediating tissue damage[22]. Epithelial cells, upon TLR stimulation, also produce T-cell homeostatic cytokines, e.g. IL-7, an important mediator of T-cell activation, IFNγ-mediated Th1 response and maintenance of pathogenic Th17 cells [23,24]). These infiltrating CD4+ T cells (Th1 and Th17) show an activated phenotype and release pro-inflammatory cytokines such as IFNγ, IL-17 and IL-6. IFNγ is involved in epithelial cell activation, apoptosis, inflammation and tissue damage[25]. IL-17 has pro-inflammatory effects on epithelial cell by induction of matrix metalloproteinases secretion, dysregulation of tight junction proteins and support of ectopic lymphoid tissues[26]. IL-6 promotes Th17 differentiation and is in turn important for the induction of IL-17.

Although the etiology of SS remains unclear, it is clear that the cytokines play a central role in the pathogenesis of SS and exhibit convergent signaling through the JAK-STAT pathway27. Therefore, the use of a JAK inhibitor may be beneficial by uncoupling the pathogenic cytokine milieu and resultant tissue dysfunction. In support of the proposed study, we have performed RNA sequencing (RNAseq) on target tissues (i.e., minor salivary gland biopsies) from SS participants and healthy volunteers.

RNAseq demonstrated enrichment of JAK- STAT pathway genes (e.g., STAT5A, STAT1, STAT2, JAK2, and JAK3) including moderate to strong positive correlation of calculated interferon scores with clinical variables of SS (e.g., focus scores, salivary flow, and the presence of autoantibodies) (Figure 1 unpublished data). Furthermore, we performed a pilot study using single cell RNAseq (scRNAseq) on minor salivary glands (MSG) from SS participants (n=3) to

investigate the transcriptional state to a single cell resolution the expression contribution of JAK-STAT pathway genes in SS participants (Figure 2 unpublished data). Expectedly, these results confirm that JAK1 and TYK2 (and to a lesser degree, JAK3), are expressed in the both the infiltrating lymphocytes and the epithelia of the gland of SS patients. These preliminary results indicate the potential for inhibiting JAK-STAT pathway may affect the pathogenic expression vectors of infiltrating cells while allowing normalization of the expression state of the secretory epithelium in salivary glands and reduction of systemic manifestations of SS.

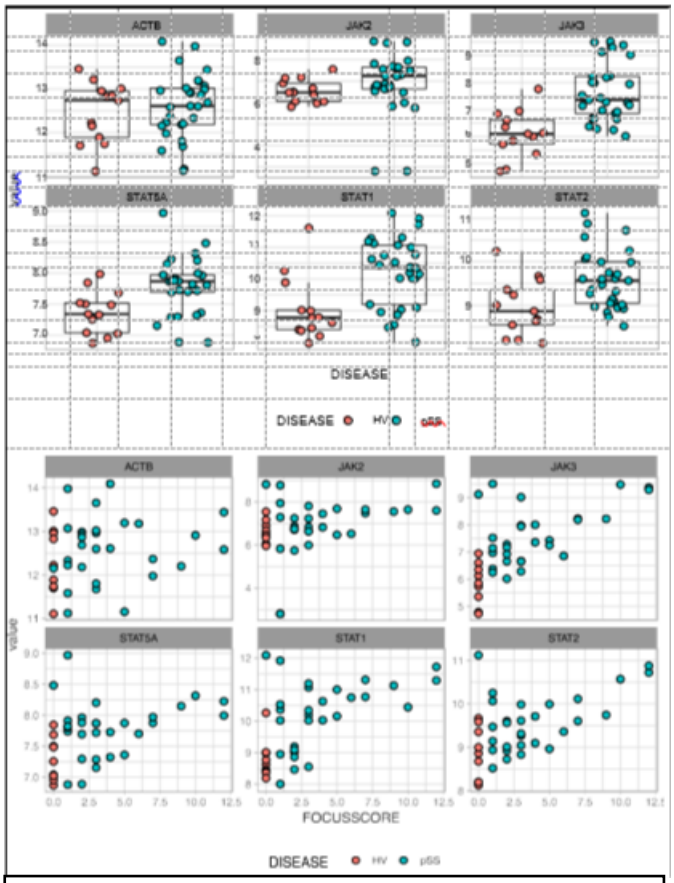


Figure 2. JAK-STAT genes upregulated in SS and correlate with Focus Score

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

Tofacitinib: Description and Summary of Clinical Studies

Tofacitinib (CP-690550; Pfizer, Inc.) is an orally administered JAK inhibitor that has recently been approved for the treatment of rheumatoid arthritis (RA), ulcerative colitis (UC), psoriatic arthritis (PsA), polyarticular juvenile idiopathic arthritis, and ankylosing spondylitis (AS). Clinical trials of Tofacitinib in RA demonstrate rapid onset of drug efficacy with an acceptable safety profile[28-32]. These clinical trials have used Tofacitinib as 1) monotherapy in participants failing non-biologic or biologic disease modifying drugs (DMARDS), 2) in combination with methotrexate in participants failing methotrexate or TNF inhibitors. The combined results are shown in

Table *1*.

Table 1. Proportion of Participants with American College of Rheumatology Response (20/50/80) Percent

Monotherapy in Nonbiologic or Biologic DMARD Inadequate Responders[c]				MTX Inadequate Responders[d]			TNF Inhibitor Inadequate Responders[e]		
Study I				Study IV			Study V		
	PBO	Tofacitinib 5 mg Twice Daily	Tofacitinib 10mg Twice Daily	PBO + MTX	Tofacitinib 5 mg Twice Daily + MTX	Tofacitinib 10 mg Twice Daily + MTX	PBO + MTX	Tofacitinib 5 mg Twice Daily + MTX	Tofacitinib 10 mg Twice Daily + MTX
N[a]	122	243	245	160	321	316	132	133	134
ACR20									
Month 3	26%	59%	65%	27%	55%	67%	24%	41%	48%
Month 6	NA[b]	69%	70%	25%	50%	62%	NA	51%	54%
ACR50									
Month 3	12%	31%	36%	8%	29%	37%	8%	26%	28%
Month 6	NA	42%	46%	9%	32%	44%	NA	37%	30%
ACR70									
Month 3	6%	15%	20%	3%	11%	17%	2%	14%	10%
Month 6	NA	22%	29%	1%	14%	23%	NA	16%	16%

[a] N is number of randomized and treated participants.
[b] NA Not applicable, as data for placebo treatment is not available beyond 3 months in Studies I and V due to placebo advancement.
[c] Inadequate response to at least one DMARD (biologic or nonbiologic) due to lack of efficacy or toxicity.
[d] Inadequate response to MTX defined as the presence of sufficient residual disease activity to meet the entry criteria.
[e] Inadequate response to a least one TNF inhibitor due to lack of efficacy and/or intolerance.

Improvement with doses of 5 mg twice daily was noted as early as two weeks, with American College of Rheumatology (ACR) 20 responses reported in 41-59% and 51- 69% of participants at three (3) and six (6) months respectively. Similarly, ACR 50 responses were reported in 26-31% and 32-42% of participants at three (3) and six (6) months respectively. Similarly, Tofacitinib use in PsA also showed a rapid onset of drug efficacy with acceptable safety profile[33, 34]. These clinical trials have used Tofacitinib in combination with a stable dose of nonbiologic DMARD (like methotrexate) and the results are summarized in **Table 2** and **Table 3** below:

Table 2 Proportion of Participants with an ACR Response in Study PsA-I [Nonbiologic DMARD Inadequate Responders (TNF Blocker-Naïve)]

Treatment Group	Placebo	Tofacitinib 5 mg Twice Daily		Tofacitinib 10 mg† Twice Daily	
N‡	105	107		104	
	Response Rate	Response Rate	Difference (%) 95% CI from Placebo	Response Rate	Difference (%) 95% CI from Placebo
Month 3					
ACR20	33%	50%	17.1 (4.1, 30.2)	61%	27.2 (14.2, 40.3)
ACR50	10%	28%	18.5 (8.3, 28.7)	40%	30.9 (19.9, 41.8)
ACR70	5%	17%	12.1 (3.9, 20.2)	14%	9.7 (1.8, 17.6)

Table 3 Proportion of Participants with an ACR Response in Study PsA--II* (TNF Blocker Inadequate Responders)

Treatment Group	Placebo	Tofacitinib 5 mg Twice Daily		Tofacitinib 10 mg† Twice Daily	
N‡	131	131		132	
	Response Rate	Response Rate	Difference (%) 95% CI from Placebo	Response Rate	Difference (%) 95% CI from Placebo
Month 3					
ACR20	24%	50%	26.0 (14.7, 37.2)	47%	23.3 (12.1, 34.5)
ACR50	15%	30%	15.3 (5.4, 25.2)	28%	13.5 (3.8, 23.3)
ACR70	10%	17%	6.9 (-1.3, 15.1)	14%	4.5 (-3.4, 12.4)

Participants with missing data were treated as non-responders.
* Participants received one concomitant nonbiologic DMARD.
† The recommended dose of Tofacitinib is 5 mg twice daily.
‡ N is number of randomized and treated participants

In general, Tofacitinib was well tolerated. The most common toxicity reported was infection with an overall frequency of 20% in participants who received Tofacitinib 5mg twice daily and 18% in the participants who received placebo. The most commonly reported infections were upper respiratory infections (URI), throat infections and urinary tract infections. Serious infections, pneumonia, cellulitis, Herpes zoster, and urinary tract infections due to bacterial or opportunistic organisms (Herpes simplex, Cytomegalovirus, Cryptococcus, Pneumocystis, and Candida) were observed in 0.4% of participants who received drug for three (3) months or less. Other toxicities, including malignancy and gastrointestinal perforation were rare. Laboratory

abnormalities, including lymphopenia, neutropenia, anemia, increased transaminases and elevated high density lipoprotein (HDL) and low density lipoprotein (LDL) were also considered mild and reversible. The lymphopenia (ALC<500 cells/mm3) was associated with an increased risk of infection but the neutropenia was not. Pooled data from 2 open-label long-term extension studies involving 4102 participants treated for 5963 participant-years reported a cardiovascular events incidence rate range from 0.05-0.3 per 100 participant-years [35]. Increase in serum creatinine of more than 50% from baseline was observed in 3.3 % of the participants[35]. The safety profile observed in participants with active psoriatic arthritis treated with Tofacitinib was consistent with the safety profile observed in RA participants [33, 34].

Recently, our collaborators at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) successfully completed a double-blind randomized placebo- controlled trial of Tofacitinib 5 mg BID in patients with Systemic Lupus Erythematosus (SLE). In this trial 20 participants with mild to moderate SLE took Tofacitinib for 8 weeks. Overall, patients with SLE tolerated Tofacitinib well with no withdrawal due to drug intolerance. Most of the adverse events were mild to moderate infections, which either self-resolved or treated with short course of oral antibiotics (Table 3). No Herpes zoster reactivation or venous thromboembolic events were recorded during the study.
Other safety parameters, including hemoglobin, total white blood cell count and liver function tests, did not show any clinically or statistically significant changes in participants on Tofacitinib during the study as compared to their baseline or group on placebo. There was a significant increase in HDL-C and HDL particle size in Tofacitinib- treated patients at the end of treatment phase, accompanied by significant improvements in plasma protein lecithin: cholesterol acyltransferase (LCAT) concentration and cholesterol efflux capacity. Arterial stiffness as measured by non-invasive vascular function studies decreased in the Tofacitinib-treated group but not in the placebo-treated group.

Table 4 Adverse events in clinic al trial of Tofacitinib in SLE

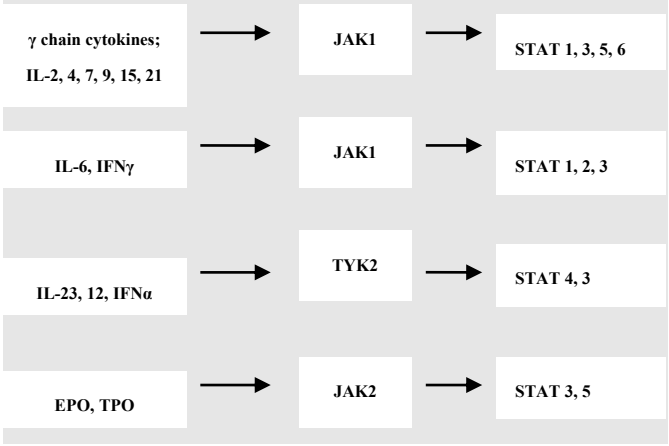
Adverse events by severity observed by treatment group			
	Tofacitinib N=43	Placebo N=28	Total N=71
Mild	32(74.4%)	23(82.1%)	55(77.5%)
Moderate	11(25.6%)	3(10.7%)	14(19.7%)
Severe	0(0%)	2(7.1%)	2(2.8%)

Tofacitinib; mechanism of action:

The JAKs are a family of intracellular enzymes (JAK1, 2, and 3, and TYK2) that facilitate signaling between inflammatory cytokines bound to surface receptors and subsequent gene transcription that regulates immune responses[36]. Specifically, JAKs phosphorylate cytoplasmic tails of cytokine receptors once the receptor has been bound by its cognate cytokine. This leads to recruitment of appropriate STAT proteins, which are in turn phosphorylated causing dimerization and disassociation from the receptor-JAK complex. STATs then translocate to the nucleus where they regulate gene transcription. Specific cytokine receptor subunit combinations selectively associate with different JAKs and STATs to differentially modulate transcription (Fig. 3). JAKs play a critical role in mediating inflammatory responses and pharmacologic

intervention modulating JAK function. This modulation represents a promising approach to the treatment of autoimmune disease including SS.

Figure 3. *Associations between JAK kinases, cytokines and STAT proteins*



Tofacitinib has been shown to inhibit JAK1, JAK2, and JAK3. Cellular assays measuring cytokine-induced STAT phosphorylation have demonstrated partial selectivity of Tofacitinib for JAK1 and 3 resulting in greater inhibition of JAK1 and 3 compared to JAK2[37]. JAK1 and JAK3 mediate intracellular responses for cytokines that use the gamma chain, which are critical for the development and function of T, B, and NK cells. Other in vitro studies suggest that the effectiveness of Tofacitinib in RA may be attributable to its suppressive effects on the generation of Th1 and pathogenic Th17 cells[38-40].
Tofacitinib also inhibits cytokines that provide B cell help such as IL-4, IL-6, and IL- 21 and can reduce B cell proliferation[41-43]. In addition, Tofacitinib inhibits the effect of IL-6 and IFN-α on innate immune cells.

Rationale for treatment with Tofacitinib:

Cytokine signaling:

Targeting JAKs is an attractive therapeutic possibility for SS for many reasons. Many of the inflammatory cytokines implicated in SS pathogenesis, in particular Type I IFNs: IL-6, IL-7, IL-12, IL-21 and IFNγ, signal through JAK/STAT pathways. These molecules mediate tissue destruction and contribute to breaking tolerance through effects on B cell activation, immunoglobulin production and expression of costimulatory molecules on lymphocytes[44,45]. Following engagement of its receptor, IFNα activates JAKs and STATs leading to increased expression of major histocompatibility complex molecules (MHC) Class I, dendritic cell maturation, T cell survival and autoantibody production[46]. Known functions of IL-6 are to enhance B cell differentiation into immunoglobulin secreting plasma cells and promote antibody production through stimulation of IL-21 by CD4+ T cells[47,48]. IL-6 is an important factor that induces naïve CD4+ cells to differentiate into Th17 cells through activation of STAT3 and induction of RAR-related orphan receptor gamma (RORγt)[49]. Additionally, anti-IL-6 monoclonal antibodies are currently being tested in clinical trials for a number of autoimmune diseases.

Positive anti-inflammatory effects of anti-IL-6 therapy are attributable, in part, to diminished support of long- lived plasma cells by IL-6. IL-17 is recognized as an important contributor to SS pathogenesis through its effects on neutrophils and monocytes and T cell migration into tissues[26]. Increased numbers of IL-17-producing T cells have been identified in SS participants and in salivary gland biopsies from SS participants [14]. IL-23 is mainly secreted by antigen presenting cells and signals through JAKs and STATs to promote expansion of IL-17 producing cells (including Th17 cells), increase IFNγ production, activate memory T cell responses and increase production of pro- inflammatory cytokines (comprehensively by Kastelein [50]). Given the importance of these pro-inflammatory cytokines that signal through JAKs and STAT proteins to the inflammatory response in SS, use of Tofacitinib has the potential to block effects of several cytokines known to exacerbate inflammatory responses in SS rather than singling out one cytokine target at a time.

T cell pathology in SS and JAK inhibition:

The importance of T cell contribution to the pathology in SS is well established[13]. The Class II MHC locus remains the strongest genetic association with SS, supporting the role of T cell-driven autoreactivity[3]. The plethora of high affinity, class-switched IgG autoantibodies characteristic of SS reflect the role of follicular T helper (T_{fh}) cells in B cell proliferation and differentiation giving rise to autoantibody producing plasma cells. T_{fh} cells are generated from naïve CD4+ T cells in the presence of IL-6, IL-21 and inducible T-Cell co-stimulator (ICOS) stimulation. Inflammation is locally driven in target organ tissue in response to cytokines that regulate vascular permeability and enhance local extravasation of inflammatory cells into tissue. Th17 cells are generated from naïve CD4+ T cells in the presence of TGFβ, IL-1β, IL-6, IL-21 and IL-23 moderating inflammatory responses by releasing the pro-inflammatory cytokines IL-17 and IL-21.

Engagement of the IL-17 receptor on target cells leads to chemokine production and results in leukocyte recruitment and production of other inflammatory cytokines such as IL-1β and TNFα. Th17-related pathology is described in multiple autoimmune diseases including RA, psoriasis, inflammatory bowel disease, SLE, and also SS[51].

Ghoreschi et al., have demonstrated, through a series of in vitro cellular assays and in vivo animal models, the range of Tofacitinib's effects on T cell function and inflammatory cytokines[38]. Tofacitinib inhibits JAK3 dependent γ_c cytokine receptor signaling and other JAK1 dependent cytokine receptor signaling. These blocking effects manifest as decreased production of inflammatory IL-23 dependent Th17 cells. Additionally, Tofacitinib blockade of JAK1 and JAK3 inhibit Th1 and Th2 differentiation and block IL-6 signaling. In an animal model of collagen-induced arthritis, mice experienced a significant reduction in established arthritis within 48 hours of treatment with Tofacitinib. Circulating inflammatory markers decreased within 4 hours, demonstrating a remarkably fast onset of action. These immediate results were not associated with leukocyte depletion. Histologic confirmation of leukocyte depletion took seven (7) days.

Others have demonstrated that treatment of human participants with Tofacitinib for prevention of graft rejection after kidney transplant results in a differential effect of Tofacitinib on T_{reg} cells and Th1 effector cells where the Th1 effector cells proved more susceptible to JAK blockade[52]. These studies have direct implications for the use of JAK inhibition in SS where, similar to the

positive results demonstrated in RA, we predict that inhibition of signaling molecules with broad effects on inflammatory responses will prove to be beneficial.

Tofacitinib likely targets pathogenic inflammatory pathways involved in the development and maintenance of SS. Additional rationale for a Phase Ib-IIa study of Tofacitinib in SS is the exploration of the inhibition of cytokines that may serve a protective role in SS. For example, IL-2 is an important immunoregulatory cytokine that promotes immune response but it is also important for peripheral tolerance[53].

IL-2 promotes expression of Foxp3 in regulatory T (T_{reg}) cells. It also inhibits IL-17 production and Bcl6 expression; Bcl6 is important for T_{fh} cells and germinal center formation. Although no evidence exists in mouse models or in humans treated with Tofacitinib that this drug promotes autoimmunity, this remains a theoretical possibility. In addition, Tofacitinib can weakly inhibit JAK2 and thereby interfere with the action of erythropoietin, GM-CSF and IL-7. Consequently, Tofacitinib could theoretically exacerbate the anemia and lymphopenia associated with SS.

Tofacitinib treatment is also associated with higher rates of BK virus nephropathy. Hence there is a possibility of BK virus activation leading to clinically significant disease after starting study participants on Tofacitinib. We will include assessment of BK virus infection at baseline and throughout the study for an additional safety measure.

2.4 RISK/BENEFIT ASSESSMENT

2.4.1 Risks/discomforts associated with Tofacitinib

Tofacitinib is approved by the Food and Drug Administration (FDA) for treatment of rheumatoid arthritis, psoriatic arthritis and ulcerative colitis. However, on September 1, 2021, based on a completed review of a large, randomized safety clinical trial, the FDA concluded that there is an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death with the arthritis and ulcerative colitis medicines Tofacitinib. This lead to the requirement of a ***"Boxed Warning"*** as follows:

Boxed Warning

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE), AND THROMBOSIS

Increased risk of serious bacterial, fungal, viral, and opportunistic infections leading to hospitalization or death, including tuberculosis (TB).

Higher rate of all-cause mortality, including sudden cardiovascular death with Tofacitinib vs. TNF blockers in rheumatoid arthritis (RA) patients.

Malignancies have occurred in patients treated with Tofacitinib. Higher rate of lymphomas and lung cancers with Tofacitinib vs. TNF blockers in RA patients.

Higher rate of MACE (defined as cardiovascular death, myocardial infarction, and stroke) with Tofacitinib vs. TNF blockers in RA patients.

Thrombosis has occurred in patients treated with Tofacitinib. Increased incidence of pulmonary embolism, venous and arterial thrombosis with Tofacitnib vs. TNF blockers in RA patients.

Notwithstanding, tofacitinib is generally well-tolerated in individuals with Rheumatoid Arthritis. The data on adverse events associated with exposure to Tofacitinib are gathered from two Phase II and 5 Phase III multi-center, double-blind, placebo controlled clinical trials where participants were randomized to Tofacitinib 5 mg twice daily, 10 mg twice daily or placebo, with or without concomitant disease modifying drugs (DMARDS); most commonly methotrexate. Adverse events associated with Tofacitinib included the following:

Infections

Tofacitinib increases the risk of serious bacterial, fungal, viral, and opportunistic infections leading to hospitalization or death, including tuberculosis (TB). In the rheumatoid arthritis (RA) studies, the overall frequency of infections was 20% in participants who received Tofacitinib 5 mg twice daily and 18% in participants who received placebo. The most commonly reported infections were upper respiratory infections, throat infections and urinary tract infections. The most serious side effects reported with Tofacitinib in RA participants were serious infections due to bacterial, viral, or fungal organisms. These occurred in 11 out of 2685 participants (0.4%) who received drug for three (3) months or less. For participants who experienced 0-12 months of exposure to Tofacitinib, serious infections were reported in 34 participants on the 5 mg twice daily dose and in 33 participants on the 10 mg twice daily dose. The most common serious infections were pneumonia, cellulitis, herpes zoster, and urinary tract infections. Tuberculosis was not reported in participants on any dose of Tofacitinib for less than three (3) months. During 0-12 months of exposure to Tofacitinib, tuberculosis cases were reported in 0 participants receiving the 5 mg twice daily dose and 6 participants who received the 10 mg twice daily dose. Opportunistic infections were not reported in participants receiving any dose of Tofacitinib for less than three (3) months. During 0-12 months of exposure, opportunistic infections were reported in four (4) participants receiving 5 mg twice daily dosing and four (4) participants receiving 10 mg twice daily dosing; the median range for Tofacitinib exposure prior to diagnosis of an opportunistic infection was eight (8) months. These opportunistic infections included cryptococcus, pneumocystis, herpes virus, cytomegalovirus (CMV) and BK virus and most occurred in participants that were also taking corticosteroids and methotrexate.

Gastrointestinal Perforation

Rare events of gastrointestinal perforation (GIP) have been reported in clinical studies of Tofacitinib in RA participants although the role of JAK inhibition in these events is not known. The estimated crude rate of gastrointestinal perforations are very low at 1.29 per 1000-person years on Tofacitinib (Xie, 2017). Although slightly higher risk than other biologics used in RA such as rituximab, the rate differences compared with various biologics used for RA remain very low and appreciably similar (range: 1-3 events per 1000 person-years). Moreover, those patients with an increased for GIP tended to be older, had pre-exiting gastrointestinal problems (diverticulosis), and prednisone use >7.5 mg/day.

Malignancy

Malignancies were reported in clinical studies of Tofacitinib. However, these rates are similar to those seen in the general population and generally stable with increasing dose56.A noteworthy exception is that higher rates of lung cancer and lymphoma were observed in trials with Tofacitinib compared with TNF blockers in RA. In a meta-analyses, there were no apparent or consistent association between tofacitinib dose and risk of malignancy except for non-melanoma

skin cancer in a long-term extension cohort57. However, numerically higher rates for all malignancies, including breast cancer and lymphoma, were observed with the higher 10 mg twice daily dose in a phase III study, but not in the long term extension cohort57. Therefore, at the 5 mg twice daily dose, currently available evidence does not indicate a significantly increased risk of malignancy in RA, the largest collective cohort of patients treated with Tofacitinib. In one post marketing study of 5,677 adult patients who participated in phase II, phase III, and long-term efficacy studies of Tofacitinib, 107 patients developed malignancies (excluding non- melanoma skin cancer). The most common malignancies were lung cancer (n = 24), followed by breast cancer (n = 19), lymphomas (n = 10), and gastric cancer (n = 6) 57.

However, it is noteworthy that Sjögren's syndrome patients have an increased risk of lymphoma development58. This is exemplified in a focused case-matched control analysis by Mariette et al., examining the incidence rates (IR; events per 100 patient-years) and standardized incidence ratios (SIRS) with respect to risk of lymphoma56. Among 19 Tofacitinib studies (Phase I [n=2], Phase II [n=9], Phase III [n=6], and long-term extension [n=2]) in patients with moderate-to-severe rheumatoid arthritis, there were 19 lymphomas in 19,406 patient-years of exposure (IR – 0.10) and the SIR was 2.656. More patients with lymphomas had a history of Sjögren's syndrome in the context of rheumatoid arthritis and were commonly positive for Anti-cyclic citrullinated peptide (anti-CCP). These results indicate that there are minimal differences in lymphoma risk for Tofacitinib across all doses and that the increased risk reported likely reflects the background disease-specific risk attributable to Sjögren's syndrome. However, we acknowledge that we do not yet know the risk of Tofacitinib administration on lymphomagenesis in Sjögren's syndrome patients.

Thus, very close clinical follow up in this patient cohort for any changes in patient status is essential and will be provided to participants.

Thrombosis:

Thrombosis, including pulmonary embolism (PE), deep venous thrombosis (DVT), and arterial thrombosis, have occurred in patients treated with Tofacitinib and other Janus kinase (JAK) inhibitors used to treat inflammatory conditions. Many of these events were serious and some resulted in death.

Patients with rheumatoid arthritis 50 years of age and older with at least one cardiovascular risk factor treated with Tofacitinib at both 5 mg or 10 mg twice daily compared to TNF blockers in RA Safety Study 1 had an observed increase in incidence of these events. The incidence rate of DVT per 100 patient-years was 0.22 for Tofacitinib 5 mg twice a day, 0.28 for Tofacitinib 10 mg twice a day, and 0.16 for TNF blockers. The incidence rate of PE per 100 patient-years was 0.18 for Tofacitinib 5 mg twice a day, 0.49 for Tofacitinib 10 mg twice a day, and 0.05 for TNF blockers.

In a long-term extension study in patients with UC, five cases of pulmonary embolism were reported in patients taking Tofacitinib 10 mg twice daily, including one death in a patient with advanced cancer.

The 10mg twice daily dose of Tofacitinib is not approved for RA and we plan to use only the 5mg twice daily regimen for this trial. Additionally, patients at high risk or a history of arterial or venous thrombosis will be excluded from the study.

Higher rates of Major Adverse Cardiovascular Events (MACE)

MACE (i.e., cardiovascular death, myocardial infarction, and stroke) was higher with Tofacitinib vs. TNF blockers in RA patients.

In an RA safety study, RA patients who were 50 years of age and older with at least one cardiovascular risk factor treated with Tofacitinib 5 mg twice daily or Tofacitinib 10 mg twice daily had a higher rate of major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke, compared to those treated with TNF blockers. The incidence rate of MACE per 100 patient-years was 0.91 for Tofacitinib 5 mg twice a day, 1.11 for Tofacitinib 10 mg twice a day, and 0.79 for TNF blockers. The incidence rate of fatal or non-fatal myocardial infarction per 100 patient-years was 0.36 for Tofacitinib 5 mg twice a day, 0.39 for Tofacitinib 10 mg twice a day, and 0.20 for TNF blocker. Patients who are current or past smokers are at additional increased risk.

Laboratory Abnormalities

- Lymphopenia: Lymphopenia below 500 cells/mm^3 occurred in 0.04 % of participants in both dosing groups of Tofacitinib within the first 3 months. Low lymphocyte counts (<500 cells/mm^3) were associated with increased risk for serious infections.
- Neutropenia: Neutropenia with an ANC less than 1000 cells/mm^3 occurred in 0.07% of participants in both dosing groups of Tofacitinib during the first 3 months of exposure. No ANCs less than 500 cells/mm3 were reported and there was no clear association between neutropenia and risk of infection. The neutropenia was dose related and reversible.
- Anemia: Although JAK inhibition has potential to affect hematopoiesis through interruption of cytokine-induced regulation of hematopoiesis, minimal effects of Tofacitinib 5 mg twice daily have been observed in the clinical trials in RA. Mild fluctuations in hemoglobin were not different from those observed in the placebo group.
- Liver Function Tests: Increased liver enzyme tests greater than 3 times the upper limit of normal were seen in approximately 1.2% of participants overall. No differences in the incidence of AST or ALT elevations were observed between the placebo, 5 mg and 10 mg twice daily groups in the first three months.
- Serum Creatinine: In a pooled analysis of five (5) phase III and two (2) long term extension studies of Tofacitinib in participants with RA increase in serum creatinine was seen predominantly in the first three (3) months of treatment. The serum creatinine increases at Month three (3) were 0.07 and 0.08 mg/dl for 5 and 10 mg twice daily (BID) Tofacitinib doses, respectively, compared with 0.04 mg/dl in the placebo. In the Tofacitinib 5 mg BID group, 17/1,220 (1.4%) participants had a confirmed serum creatinine increase of 33% from baseline in Months 0 to 3. Of these participants, only two (2) had serum creatinine elevation above the reference range for normal. In the Tofacitinib 10 mg BID group, 23/1,217 (1.9%) participants had a confirmed serum creatinine increase 33% from baseline in Months 0 to 3. Of these 23 participants, only four (4) had serum creatinine above the reference range for normal. No continued worsening of serum creatinine was noted during the long-term follow-up studies. The published data

revealed that these changes plateaued or reversed in long term follow up.

- Lipids: Dose related elevations of lipid parameters were observed at one month of exposure and remained stable thereafter. These were:
- A mean increase of LDL by 15% in the 5 mg twice daily arm and 19% in the 10 mg twice daily arm, and
- A mean increase in HDL by 10 % in the 5 mg twice daily arm and 12% in the 10 mg twice daily arm.

However, mean LDL/HDL ratios were unchanged in participants treated with Tofacitinib.

Other Adverse Reactions

Other adverse reactions reported with Tofacitinib at doses of 5 mg BID include diarrhea (4%), nasopharyngitis 3.8%), upper respiratory infections (4.5%, headache (4.3%), high blood pressure (1.6%). None of these occurred significantly more frequently than in the participants who were treated with placebo.

Medication Interactions

Serum Tofacitinib levels can increase when it is co-administered with moderate and potent inhibitors of cytochrome P450 (CYP) 3A4 (e.g., ketoconazole) or CYP2C19 (e.g., fluconazole). Potent CYP3A4 inducers (e.g., rifampin) will decrease exposure to Tofacitinib.

The risk of increased immunosuppression is enhanced if Tofacitinib is co-administered with potent immunosuppressive drugs such as azathioprine, tacrolimus, cyclosporine.

Flare of Sjögren's syndrome:

There are no data about the use of Tofacitinib in individuals with SS. Tofacitinib may be ineffective or may even worsen SS. The potential impact of flares is minimized in this study by close monitoring of participants and strict withdrawal criteria for flares.

2.4.2 Risks associated with study procedures

Minor Salivary Gland Biopsy

The biopsy will be performed according to NIDCR SOPs. Local anesthetic will be administered to minimize pain during the procedure. Biopsy of the MSG may cause discomfort, pain, and swelling at the site (usually lower lip) for several days following the procedure; these symptoms can be effectively treated with ibuprofen, acetaminophen, or more potent analgesics as needed. Participants may also experience transient paresthesia in the region of the biopsy, permanent paresthesia, although reported, are exceedingly rare using the techniques employed by the NIDCR. Other possible risks are allergic reactions to the local anesthetic and bleeding and infection at the site of biopsy however, such events are rare.

In a retrospective analysis of biopsies performed in our Clinic, aphthous ulcers developed in less than 5% of volunteers who participated in our study. Although the exact cause was not identified, this is well-known risk associated with the mucosal biopsy and anesthetic injection. Post-operative checks are routinely accomplished 4 to 7 days after the procedure for suture removal. Typically, resorbable sutures are used and no follow up is necessary. Rarely a

participant will have defective healing, forming an epithelial tag or mucocele. These are surgically correctable and will be addressed by an NIDCR dentist or oral surgeon.

Salivary Gland Ultrasound

There are no known risks of salivary gland ultrasounds. This procedure is generally considered safe. Patients may experience slight discomfort (cold feeling of the skin) on the areas of the face where transduction gel is applied.

Collection of Saliva/Measurement of Salivary Flow Rate

There is no known risk associated with this salivary collection. Participants may experience mild discomfort due to increased dryness caused by withholding salivary stimulants for 24 hours prior to saliva collection. There may be mild discomfort due to positioning of mouth during saliva collection. Citric acid (lemon juice) solution used to stimulate salivary flow may cause an unpleasant taste and mild discomfort in the salivary glands if the parotid duct is blocked and saliva cannot be expressed.

Vascular function studies: SphygmoCor, CAVI and Endopat

There is no known risk of these procedures. The procedures are very well tolerated, other than potential minimal transient discomfort associated with the inflation of the blood pressure cuff; no side effects are expected.

Dry Eye Examination

An ophthalmologist measures eye pressure and examines the front part of the eye. Anesthetic eye drops will be used in order to measure eye pressure. Occasionally there may be a local allergic reaction to any medication such as the anesthetic eye drops. If this should occur, appropriate medication to control the allergic reaction will be administered.

Schirmer's test performed to evaluate adequate tear production, and MMP-9 simple strip to assess presence (positive/negative) of inflammatory protein may be uncomfortable but should not be painful.

Blood draws

Participants may experience discomfort, bleeding, or bruising at the venipuncture site, which should resolve with time. There is also a small risk of fainting. Infection at the site of needle insertion may also occur but is rare with the use of sterile disposable needles and aseptic technique.

The amount of blood drawn for clinical care indication and research purposes will be kept within the NIH guidelines of 10.5 mL/kg or 550 mL, whichever is smaller, over any 8-week (56 days) period for adults.

2.4.3 Known potential benefits

There may be no direct benefits to participants. Participants may benefit from a thorough evaluation by experts in SS.

Although the primary endpoint is safety in this double-blind placebo-controlled study, there is the possibility that potential participants with mild to moderate disease activity in SS,

randomized to drug, may derive a medical benefit. However, this may be a temporary effect while patients are on drug and long-term benefits are not anticipated.

2.4.4 Alternatives to participation or other therapies

The alternative to study participation is conventional treatment. There are limited treatment options available for SS participants with mild to moderate disease activity including higher doses of corticosteroids; switching to or adding another immunosuppressant; hydroxychloroquine.

2.4.5 Assessment of known potential risks and benefits

Unforeseen adverse effects are a risk with every new drug treatment, including new indications for approved drugs. The risks of participating in this study are reasonably relative to the potential health benefits and generalizable medical knowledge that may be obtained.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	JUSTIFICATION FOR ENDPOINTS	ENDPOINTS
Primary		
To determine the safety and tolerability of Tofacitinib in participants with SS and mild to moderate disease activity.	This is an FDA approved drug that is not currently approved for use in the Sjögren's syndrome population. Tofacitinib has demonstrated both clinical and molecular potential to be an effective treatment for SS, however studies are lacking in this research population.	Safety and tolerability will be measured by assessment of adverse events (AEs) and clinical safety laboratory tests throughout the study. Toxicity is defined as any study drug-related Grade 3 or higher adverse event, as measured by the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0).
Secondary		
To assess clinical improvement after treatment with Tofacitinib as measured by no change or improvement in the ESSDAI and no worsening on the physician's global PGA.	The ESSDAI was developed to be used as an outcome measure in clinical trials involving Sjögren's syndrome patient cohorts. It allows for assessment/scoring of major domain activity relevant to a SS population.	Assessments of clinical response will be measured by: 1) the change in ESSDAI between baseline and study day 168 2) No worsening of PGA between baseline and study day 168
To demonstrate that treatment with Tofacitinib is effective clinically and biologically in SS individuals with mild to moderate disease.	Data from a randomized placebo-controlled trial of Tofacitinib in SS would yield evidence to further pursue JAK/STAT pathway targeting in SS. Salivary flow rates are an objective measure of organ	Change in salivary flow rates between baseline and study day 168

OBJECTIVES	JUSTIFICATION FOR ENDPOINTS	ENDPOINTS
	function. Low salivary flow is a primary feature of SS and may be used as a non-invasive measure of therapeutic intervention.	
To investigate the effects of Tofacitinib on systemic biomarkers of SS as measures of biological effects that can be used as outcome measures to power a larger Clinical Trial.	The biological effects of Tofacitinib in this research population are unknown. Assessing for changes in major biological markers of SS will improve the understanding and potential uses of Tofacitinib in this and other disease states.	Changes in serum cytokines, autoantibody levels (e.g., ANA-Hep2 substrate, SSA, SSB autoantibody titers), complement proteins C3 and C4, markers of systemic inflammation such as ESR and CRP between baseline and study day 168
Tertiary/Exploratory		
Identify transcriptional changes in affected tissues due to JAK-STAT inhibition.	Target tissue (MSG) transcriptional landscape changes from baseline to Day 168 with respect to treatment allocation.	Transcriptional alterations and pathway analysis using RNA sequencing (RNAseq) on MSG and/or peripheral blood mononuclear cells (PBMC) between baseline and study day 168. Transcriptional and tissue compositional changes using single cell (sc)RNAseq on available tissue collected between baseline and study day 168.
Assess target tissue histopathological and architectural changes as a correlative measure with functional improvement.	Target tissue (MSG) changes in immune infiltration histopathology from baseline to Day 168 with respect to treatment allocation.	Change in MSG biopsy histopathology including focus score, infiltrate area, acinar density, and fibrosis.
Identify changes in infiltrating immune cells and the correlation with other markers of effect.	Target tissue (MSG) changes in immune infiltration from baseline to Day 168 with respect to treatment allocation.	Immunophenotyping of immune cell infiltrates in minor salivary gland biopsies by immunohistochemistry. We will specifically focus on numbers and or density of CD+3, CD20+, CD8+, CD4+, CD25+, Foxp3+ regulatory subsets and Th17 cells.
Identify changes in infiltrating immune cells and the correlation with other markers of effect.	Target tissue (MSG) changes in immune infiltration from	When tissue is available, alteration in minor salivary gland immune cell

OBJECTIVES	JUSTIFICATION FOR ENDPOINTS	ENDPOINTS
	baseline to Day 168 with respect to treatment allocation.	populations by flow cytometry with attention to CD3+, CD20+ NK, CD8+, CD4+, CD19+, CD25+, Foxp3+ regulatory subsets.
Identify changes in circulating immune cells and the correlation with other markers of effect.	Peripheral blood immune compositional measures from baseline to Day 168 with respect to treatment allocation.	Alteration in peripheral blood immune cell populations by flow cytometry with special attention to NK, CD8+, CD4+, CD25+, Foxp3+ regulatory subsets and Th17 cells.
Quantify the effect of JAK-STAT pathway inhibition in patient tissues.	Peripheral blood measures of JAK/STAT pathway activation state from baseline to Day 168 with respect to treatment allocation.	Ligand-induced STAT phosphorylation in circulating T cells and monocytes using phosphoflow assessment of single cells.
Quantify the effect of JAK-STAT pathway inhibition on circulating cytokine expression.	Changes in peripheral blood inflammatory biomarkers from Baseline through Day 168 with respect to treatment arm allocation.	Measures of serum cytokines (like IL-2, 4, 6, 7, 9, 15, 12,17, 23, TNFa, TNFb, IFNα and IFNγ)
Changes in lacrimal function	Ocular and lacrimal effects are main clinical complaints in SS. Improvement would reflect reduced pathogenic inflammation or cytokine expression in the lacrimal glands and reciprocal improvement in ocular surface characteristics or lacrimation from Baseline through Day 168 with respect to treatment arm allocation.	Change in corneal surface staining, changes in Schirmer's.
Assess measures of cardiovascular status.	Measures of cardiovascular health were improved in a recent clinical trial of Tofacitinib in SLE patients. We are interested in the SS cohort from Baseline through Day 168 with respect to treatment arm allocation.	In addition to the routine lipid profile, we may also perform measurements of lipoproteins, including nuclear magnetic resonance (NMR) profile and cholesterol efflux capacity that have been associated with differences in atherosclerotic

OBJECTIVES	JUSTIFICATION FOR ENDPOINTS	ENDPOINTS
		risk in autoimmune diseases between baseline and study day168.
Assess changes in insulin resistance.	Insulin resistance changes may inform effects on systemic health and cardiovascular health.	Change in insulin resistance between baseline and study day 168.
To investigate the effects of Tofacitinib on participant quality of life measures.	Patient-reported outcomes are a way to quantitatively assess therapeutic effects of a given intervention. There is a need for participative and objective effectiveness data of Tofacitinib in our research population.	Patient reported outcomes for clinical efficacy will be measured by changes assessed by ESSPRI, 2002 AECG Subjective Symptom Questionnaire, Subject dry mouth questionnaire, OHIP-14, Xerostomia VAS, FSS, PROMIS, and the Short Form 36 health survey between baseline, study days 96, and 168.
To investigate the effects of Tofacitinib in modulation of endothelial responses and markers of vascular risk in SS as a benefit of improved vascular function.	A recent trial of Tofacitinib in SLE patients showed a decrease in vascular/ endothelial stiffness compared to placebo. Post-marketing research has shown increased risk of PE in RA patients treated with Tofacitinib. There is a need to better understand the vascular effects/risks associated with this treatment.	Changes in arterial stiffness in Tofacitinib group relative to placebo between baseline and study day 168.
Changes in autoantibody levels.	Changes in autoantibodies due to treatment allocation may provide future data to perform clinical trials as surrogate endpoints of efficacy.	Changes in serum and salivary autoantibodies by light immunoprecipitation system (LIPS) between baseline and study day 168.
Changes in oral microbiome.	Changes in microbiome may reflect restoration of salivary function.	Changes in the microbial diversity of oral and salivary microbiome between baseline and study day 168.
Saliva Compositional Changes.	Changes in salivary composition may reflect changes in glandular inflammation. These changes	Change in collected salivary proteins and ionic composition as markers of improved saliva function

OBJECTIVES	JUSTIFICATION FOR ENDPOINTS	ENDPOINTS
	can be correlated with disease response and serve as potential biomarkers for future Phase III studies.	between baseline and study day 168.
Assess the durability of clinical and biological effects after cessation of therapy.	Any clinical or biological changes due to treatment may be short-lived after the cessation of therapy. Understanding the consequence of treatment withdrawal may help refine future studies and the immunology of the diseases.	Assessment of durability of the clinical and biologic effects will be measured by changes in all of the above clinical and biologic measures between study days 168 and 196 except for biopsies which will only be obtained at before baseline and at end of treatment.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase Ib-IIa, randomized, double blinded, placebo controlled clinical trial of orally administered Tofacitinib, 5 mg twice daily, for treatment of individuals with mild to moderate SS disease activity. The study will aim to screen up to 76 adult participants in order to achieve a target study of 30 participants for randomization plus up to 11 participants to replace subjects lost to attrition or early withdrawal from the study and to complete enrolment in unfilled randomization blocks. There will be two (2) study arms with 20 participants in Tofacitinib arm and 10 participants in placebo arm. The study duration is a maximum of 241 days with a 45-day screening period followed by a 168-day treatment period and a 28-day follow-up period. The study is a single-site study to be conducted in the NIH Clinical Center. The proposed clinical trial is an exploratory study designed to yield preliminary data about the safety, clinical, and biologic efficacy of Tofacitinib in SS participants with mild to moderate disease activity.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The proposed clinical trial is an exploratory study designed to yield preliminary data about the safety, and clinical and biologic efficacy of Tofacitinib in SS participants with mild to moderate disease activity. If the drug is well tolerated by SS participants, the data can be used to design and power a larger study of clinical efficacy and safety.

4.3 JUSTIFICATION FOR DOSE

As per the package insert recommendations, each participant will be dosed with 5 mg (1 tablet) twice daily for 168 days as is recommended for the treatment of rheumatoid arthritis. Tofacitinib and placebo tablets will be supplied by Pfizer Incorporated to the NIH Clinical Center Research Pharmacy.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Adult primary SS participants with mild-to-moderate disease activity will be eligible for this study. Enrolled participants can be naïve or failed immunosuppressive therapy beyond antimalarials and glucocorticoids; to prevent bias in the cohort of participants with more recalcitrant disease. We expect that Tofacitinib is a potential second line therapy, in addition to antimalarials and glucocorticoids, depending on the participant's initial presentation and response. Women and members of minority groups, if eligible, will be included in accordance with the NIH Policy on Inclusion of Women and Minorities as Participants in Research Involving Human Participants.

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Ability of participant to understand and the willingness to sign a written informed consent document.
2. Participation and enrollment in companion protocol, 15-D-0051, Characterization of Diseases with Salivary Gland Involvement.
3. Stated willingness to comply with all study procedures and availability for the duration of the study
4. Male or female, aged between 18-75 years
5. In good general health as evidenced by medical history
6. Meets the 2002 American European Consensus Group classification criteria for primary Sjögren's Syndrome or 2016 American College of Rheumatology/European League against Rheumatism Classification Criteria (ACR-EULAR) with mild to moderate disease activity defined as ESSDAI between 0 to 13 at the screening visit and >0 ml/min/gland stimulated saliva flow.
7. Ability to take oral medication and be willing to adhere to the study intervention regimen
8. If on glucocorticoids, the dose must be less than 10 mg daily and stable for the 4 weeks (28 days) prior to screening visit.
9. If on hydroxychloroquine or other antimalarials such as chloroquine or quinacrine, the dose must have been stable for the 12 weeks (96 days) prior to screening visit. The maximum allowed dose is hydroxychloroquine up to 400 mg/day or 6.5 mg/kg/day if more than 400 mg/day. The maximum allowed dose for chloroquine phosphate is up to 500 mg daily and for quinacrine up to 100 mg daily.
10. Participants may be on lipid lowering medications if initiated at least 3 months prior to the screening visit and dose must be stable for 4 weeks (28 days) prior to study entry.
11. Males and females with potential for reproduction must agree to practice effective birth control measures. Females should be on adequate contraception if they are of child-bearing potential documented by a clinician, unless participants or spouse have previously undergone a sterilization procedure. Adequate birth control measures are: intrauterine device (IUD) alone or hormone implants, hormone patches, injectable, or oral contraceptives plus a barrier method (male condom, female condom or diaphragm), abstinence or a vasectomized partner.

12. Agreement to adhere to Lifestyle Considerations (see section 5.4) throughout study duration

5.2 EXCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must not meet any of the following criteria:

1. Current or prior treatment with rituximab, belimumab or any other biologic agent in the 6 months prior to screening.
2. Current treatment with methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, or other less common immunomodulatory drugs such as those falling into the class of disease-modifying antirheumatic drugs (DMARDs), not otherwise specified herein. Participants previously on methotrexate, azathioprine, mycophenolate mofetil, cyclosporine or tacrolimus, or other DMARDs should have withdrawn drug for at least 8 weeks (56 days) at the time of screening.
3. Treatment with cyclophosphamide, pulse methylprednisolone or IVIG within 6 months prior to screening.
4. Current treatment with potent inhibitors of Cytochrome P450 3A4 (CYP3A4) (e.g., ketoconazole) or receiving one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole) that would increase serum availability of Tofacitinib. Past treatment with the aforementioned agent is allowed if it was more than a week prior to the administration of the first dose of study medication.
5. History of chronic liver disease, not including well-controlled Sjogren's-related chronic liver disease or elevated LFTs:
    - ALT or AST ≥ 2x upper limit of normal at screening
    - Serum unconjugated bilirubin > 2mg/dL at screening
6. Serum creatinine >1.5mg/dL.
7. Protein to creatinine ratio of more than 1mg/dL at screening (repeated and confirmed three times or confirmed with 24 hours urine protein of more than 1000 mg).
8. Active urinary sediment (WBC, RBC or mixed cellular casts 1+ or more /hpf).
9. Hypercholesterolemia: Values after 8-12 hour fasting blood specimen: total cholesterol >250 mg/dL or LDL >180 mg/dL or hypertriglyceridemia (triglyceride >300 mg/dL) within - 45 days of screening visit.
10. WBC <2500/µL or ANC <1,000/µL, Hgb <9.0 g/dL or platelets <70,000/µL or absolute lymphocyte count < 500/µL.
11. Pregnant or lactating women. Women of childbearing potential are required to have a negative pregnancy test at screening.
12. A history of drug or alcohol abuse within the 6 months prior to screening.
13. Currently receiving hemodialysis, peritoneal dialysis, or intestinal dialysis.
14. Active infection that requires the use of oral or intravenous antibiotics unresolved at least 14 days prior to the administration of the first dose of study medication.
15. Active chronic infections including but not limited to HIV, Hepatitis B, Hepatitis C, and BK viremia at screening visit.

16. Current or previous diagnosis of malignant disease, except for basal cell or squamous cell carcinoma of the skin with complete excision and clear borders or adequately treated in situ carcinoma of the cervix.
17. Known active tuberculosis. Participants with treated latent tuberculosis (LTB) will be eligible to participate. Participants with untreated LTB will not be excluded but will be evaluated by an infectious disease (I.D.) consultant and may become eligible for trial based on infectious disease consultant recommendations.
18. History of severe or systemic infection caused by common pathogens, or history of infection with pathogens that normally do not cause human disease.
19. Participants with active renal or central nervous system disease or a high activity level in any organ system (except articular) in ESSDAI[54].
20. Participants with known increased risk factors for major adverse cardiac event (MACE) including a history of:
    - Ischemic heart disease (e.g., history of acute myocardial infarction)
    - Heart failure
    - Cardiomyopathy
    - Severe valvular heart disease
    - Significant arrhythmias
    - Chronic renal failure
    - Cerebrovascular accident or transient ischemic attack
    - Uncontrolled diabetes mellitus
    - Uncontrolled hypertension
    - Current smokers or former smokers with less than 3 years since complete cessation and/or >20 pack-years of smoking history.
21. Significant impairment of major organ function (lung, heart, liver, kidney) or any condition that, in the opinion of the Investigator, would jeopardize the participant's safety following exposure to the study drug.
22. Known history of arterial or venous thrombosis or at high risk for clotting disorder
23. Psychiatric illness or history of medical non-compliance that the study team feels will make the patient unlikely to complete the study
24. Uncontrolled thyroid disease as per PI or medically responsible investigator.
25. Known allergic reactions to Tofacitinib or its components
26. Treatment with another investigational drug/intervention within six months except for COVID-19 vaccines or therapies that have been granted an FDA emergency authorization.

5.3 Inclusion of Vulnerable Participants

We do not intend to enroll the following vulnerable populations: children, pregnant women, prisoners, or decisionally-impaired adults.

Spanish speakers and patients who speak other languages may be eligible for participating in this study. We will use a Spanish translated version of the long form for enrollment of Spanish speaking participants. NIH translators will be provided at study appointments.

5.3.1 Participation of NIH Staff or family members of study team members

NIH staff and family members of study team members may be enrolled in this study as long as this population meets the study entry criteria. Neither participation nor refusal to participate as a subject in the research will have an effect, either beneficial or adverse, on the participant's employment or position at NIH.

We will follow the requirements outlined in Policy 404 Research Involving NIH Staff as Subjects, ensuring the guidelines (https://policymanual.nih.gov/3014-404) are met.

Every effort will be made to protect participant information, but such information may be available in medical records and may be available to authorized users outside of the study team in both an identifiable an unidentifiable manner.

The NIH Frequently Asked Questions (FAQs) for Staff Who are Considering Participation in NIH Research will be made available. Please see section 10.1.1 for consent of NIH Staff Lifestyle Considerations.

During this study, participants are asked to:

- Fast overnight (past midnight) for the following visits: Screen, Day 1, Day 84, Day 168 and Day 196.
- Withhold salivary stimulants for 24 hours prior to saliva collection.
- Refrain from eating or drinking anything for 1 ½ hours prior to having a saliva collection. Saliva collection is done at the following visits: Screen, Days 1, 84, 168 and 196.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomized to a study arm. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) due to failing to meet entry criteria, may be rescreened and considered for study participation. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 Strategies for Recruitment and Retention

Multiple recruitment strategies are planned using the IRB approved recruitment material. Our primary recruitment approach will be to contact participants already known to the Sjögren's syndrome NIDCR clinical protocols (15-D-0051 and 11-D-0172) where participants have consented to be contacted regarding future studies.
Additional methods for recruitment will include contacting patient support groups (e.g., Sjogren's Foundation) as well as contacting referring physician groups to advertise and potentially refer participants. We will utilize the services of NIH Clinical Center Office of Patient Recruitment and adhere to the NIH Clinical Center Media Policy. Various NIDCR social media platforms which adhere to NIH and the IC's social media guidelines may also be used.

For recruitment, the study team will ensure that social and new media applications and accounts are set up and managed in accordance with Section 508 of the Rehabilitation Act of 1973: guidance available at http://www.hhs.gov/web/508/index.html and HHS policy available at https://intranet.hhs.gov/it/strategy-policy-governance/policies-standards-guides/508-accessibility-of-technology.html. For all the recruitment strategies, we will use the approved recruitment materials.

Target Patient Samples Size by Gender and Race and Ethnicity: 30 total patients which will include approximately 27 females and 3 male participants, which reflects the typical female: male distribution of patients in our clinic. We anticipate that 10% of our participants will be non-white reflecting our current racial-ethnic distribution in our clinic.

Participants may also be recruited:

- Outpatient Sjögren's syndrome and Salivary Disorders Clinic, or Rheumatology Clinic of the Clinical Center at the NIH or the NIAMS Community Health Center;
- Participants referred for treatment and/or second opinion to the NIH;
- Local area rheumatologists, internists, dental practices, and university hospital clinics;
- Participants that are referred by their local providers, we will requested to contact the research coordinator directly to initiate a release of medical records for review for study eligibility. Consistent with our current research protocols in this study population, we expect the sending provider has obtained a signed HIPAA authorization or other type of signed medical release of information (if under the Privacy Act or outside of the US) to be able to share these records or specimens with the study coordinator.

5.5.1 Recruitment of women, children, and minorities:

Minors and pregnant women will not be included in this study. This is a Phase Ib-IIa study involving greater than a minor increment over minimal risk without the prospect of direct benefit to participants based on currently available data. The sex distribution (female: male) for SS is 9:1; recruitment is expected to support this distribution.

5.5.2 Costs

We do not anticipate any direct costs for study participation.

5.5.3 Compensation

Participants will receive financial compensation for time required to participate in the research as per NIH guidelines. The participants will be paid $130 at each outpatient visit. In addition, participants will be paid an additional $100 at the end of study visit Day 196 as a study completion bonus. Patients who receive a second (or additional non-diagnostic biopsy) biopsy will be paid $220 for each additional salivary gland biopsy. Any participant who withdraws from study will be paid for the number of visits completed. For participants living outside a 45-mile radius, travel compensation may be provided at discretion of the principal investigator.

Meal cost will be reimbursed up to $50.00 USD a day per participant per study visit for participants travelling from outside a 45-mile radius to the Clinical Center.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTIONS(S) ADMINISTRATION

Tofacitinib (Pfizer, Inc.) is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes that transmit signals arising from cytokine or growth factor-receptor interactions on immune cell membranes to influence cellular processes of haematopoiesis and immune cell function. Within the signalling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Tofacitinib modulates the signalling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs.

Tofacitinib citrate is a white to off-white powder with the following chemical name: (3R,4R)-4-methyl-3-(methyl-7H-pyrrolo [2,3-d]pyrimidin-4-ylamino)-β-oxo-1- piperidinepropanenitrile, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) It is freely soluble in water and has a molecular weight of 504.5 Daltons. Tofacitinib is supplied for oral administration as 5 mg white round, immediate-release film-coated tablets. Each tablet of Tofacitinib contains the appropriate amount of Tofacitinib citrate salt and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, HPMC 2910/Hypromellose 6cP, titanium dioxide, macrogol/PEG3350, and triacetin.

There will be no IND obtained for the use of any of the investigational agents used in this study.

This study meets the criteria for exemption for an IND as this investigation is not intended to support a new indication for use or any other significant change to the labeling; the drugs are already approved and marketed and the investigation is not intended to support a significant change in advertising; and the investigation does not involve a route of administration or dosage level in use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product. The Food and Drug Administration was contacted on 12/18/2019 for a determination for IND and approved a waiver on 01/23/2020; a copy of the FDA IND waiver for IND is provided.

6.1.1 Dosing and Administration

The package insert with the recommended dosing is provided. Each participant will be dosed with 5 mg (1 tablet) twice daily for 168 days as is recommended for the treatment of rheumatoid arthritis. Tofacitinib and placebo tablets will be supplied by Pfizer Incorporated to the NIH Clinical Center Research Pharmacy.

6.1.2 Participant Dosing Considerations

Participants entering the study will have mild to moderate disease activity. Based on the known response to Tofacitinib in RA, animal studies, and cellular assays; we expect a similar rapid response in SS participants.

- Any participants experiencing a flare of glandular or extra-glandular manifestations of Sjögren's syndrome, evaluated by the PI or the medically-responsible investigator will be re-evaluated in two (2) weeks (14 days). Study drug will be continued during the monitoring period. If disease activity continues to worsen, the participant will be withdrawn from the study as per Section 7.

- Participants with absolute neutrophil count (ANC) 500 to 1000 cells/mm3, will have study drug dosing interrupted until absolute neutrophil count (ANC) is greater than 1000 within 28 days; at that time study drug dosing will resume at 5 mg, orally, twice daily. Otherwise, participants will be withdrawn per Section 7.
- Participants with hemoglobin less than 8 g/dL or a decrease of more than 2 g/dL from baseline will have study drug dosing interrupted and held until hemoglobin values have at least returned to baseline within 28 days at which time study drug will be reintroduced. Otherwise, participants will be withdrawn per Section 7.
- Study drug may be interrupted at the discretion of the investigator if it is in the best interest of the participant.

Drug Administration

A 35-day supply of study drug or placebo will be dispensed to participants on study days 1, 28, 56, 84, 112,140 visits as well as unscheduled visits, if required with instructions regarding the twice daily dosing regimen and a review of potential side effects. No drug will be dispensed to a female participant of reproductive potential until negative pregnancy test results (serum or urine) have been obtained within 24 hours of on site visit.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Tofacitinib five (5) milligram (mg) tablets are white, round, immediate release film-coated tablets, debossed with “Pfizer” on one side and “JKI 5 on the other side. Tofacitinib tablets will be stored at 20°C to 5°C 68°F to 77°F) as per manufacturer’s recommendations included in labelling.

6.2.1 Acquisition and Accountability

Pfizer is providing seventy-count (#70) labelled bottles of 5 mg Tofacitinib and placebo. These bottles will be dispensed monthly to the study participants by pharmacy after protocol mandated visit is completed and all clinical and study parameters meet approval of the PI or AI seeing the participant.

6.2.2 Formulation, Appearance, Packaging, and Labeling

Tofacitinib tablets contain 5 mg Tofacitinib. They are white, round, immediate-release film coated tablets, debossed with “Pfizer” on one side, and “JKI 5” on the other side.

6.2.3 Product Storage and Stability

The drug and placebo will be stored in the NIH Pharmacy according to the manufacturer’s suggested storage conditions.

6.2.4 Preparation

Study drugs are provided in the expected quantity and preparation.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization will be done by the NIH Clinical Research Center Pharmacy in conjunction with the statistician associated with the study. This is a two-arm, double blind study.

The study will utilize the stratified block randomization method to ensure that the Tofacitinib and placebo groups are balanced with respect to the baseline disease activity level. Eligible

subjects will be stratified according to the ESSDAI score (0-1 vs. 2-13). Within each stratum, subjects will be randomly assigned by use of computer-generated blocks of size 3 with a 2:1 ratio to Tofacitinib or control group. Thus, participants will be randomized to either Tofacitinib or placebo in a 2:1 ratio overall. Both participants and investigators will be blinded to treatment allocation. Unblinding for analysis will occur once all the collected study data has been entered and the database is locked. Participants and local treating physicians will be informed of treatment allocation by a letter sent by certified mail, at that time.

The blind will be held by the statistician and the NIH Clinical Center Research Pharmacy. In cases where breaking the blind is necessary to provide clinical care to the participant, as determined by the PI and medically responsible team member, Sarthak Gupta, MD, the PI will contact the NIH Clinical Center Research Pharmacy and provide the treatment allocation information to the treating physician. Such participant(s) would be withdrawn from the study and followed up as described in section 4.10 above.

The Data and Safety Monitoring Committee (DSMC) may also request unblinding of treatment allocation or group assignment. These requests will be transmitted to the NIH Clinical Center Research Pharmacy by the PI. Data will be provided directly to the DSMC Chair without unblinding the investigators before the DSMC determines a plan of action.

6.4 Study Intervention Compliance

Compliance with study drug dosing will be assessed during on-site visits, at study day 28, 56, 84, 112, 140, 168 visits as well as unscheduled visits, if required. Participants will be asked to bring their bottles of study drug for a recorded pill count. Participants who have demonstrated less than 80% compliance at study visits will be withdrawn from the study. Compliance with study medication will be determined by the PI based on multiple factors, including but not limited to pill count, overall compliance with study procedures, and the reliability of self-reporting of compliance based on prior interactions. Study treatment compliance will also be assessed on telephone calls on day 7, 21, 42, 70, and 154 (+/- 3 days). A standard scripted conversation will be used for telephone calls to determine compliance with protocol requirements. Participants withdrawn from the study after receiving study treatment will be asked to follow up to complete the study days 168 and 196.

6.5 Missing study medication

Doses and loss of medication bottle are possible occurrences during the 24-week (168 day) dosing period. Missed doses will be documented at each compliance check but will not result in a protocol deviation. In the event a dispensed bottle of study drug is lost by a participant, the study team will contact pharmacy and dispense a replacement bottle to the participant. A note to file will be created describing the event in detail and the incident will be reported to Pfizer. In the event the missing study drug is found, participants will be advised to return it.

6.6 Concomitant Therapy

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.

Concomitant therapy information will be recorded at all study visits including screening.

The following medications are allowed provided that they are administered at stable doses during the study:

- Antimalarial (hydroxychloroquine 400 mg/day or ≤6.5 mg/kg/day, if more than 400 mg/day, chloroquine phosphate 500 mg daily, quinacrine 100 mg daily); must already be on stable dose of this medication 12 weeks (96 days) prior to study entry.
- Prednisone or equivalent steroid dose up to 10 mg /day must already be on stable dose of this medication four (4) weeks (28 days) prior to study entry.
- ACE (angiotensin converting enzyme) inhibitors or angiotensin receptor blocking (ARB) medications, must already be on stable dose of this medication four (4) weeks (28 days) prior to study entry.
- Prescription medications with oral drying as a known side effect, such as anti-cholinergic, anti-histamines, selective serotonin reuptake inhibitors, tricyclic anti-depressants, amphetamines, should be stable for 12 weeks (96 days) prior to screening visits.
- Lipid lowering medications if initiated at least three (3) months prior to the screening visit. The dose of any of these medications can be decreased (temporally or for the duration of the study) if clinically indicated for toxicity.

The following systemically administered medications and vaccines listed below will not be allowed during treatment. A list of prohibited medications which will be provided to the participants upon consenting will be reviewed to confirm any of those medications are included in their standard treatment regimen. Local administration of prohibited medications may be allowed in certain circumstances (e.g., Cyclosporine, locally administered corticosteroid injections) at the discretion of the PI or Medically Responsible Investigator. Any clinical indication requiring treatment with medications listed below will lead to cessation of study treatment. Withdrawn participants will be asked to return according to the follow up phase of the study and to complete all study procedures.

- Rituximab.
- Any other biologic agent including TNF-α blockers, IL-1 blocking agents, anti-IL-6 agents, belimumab, abatacept.
- Cyclophosphamide.
- Azathioprine.
- Mycophenolate mofetil.
- Rapamycin.
- Cyclosporine.*
    - Topical cyclosporine used for keratoconjunctival sicca will be permitted.
- Tacrolimus.
- Methotrexate.
- Administration of any live virus vaccines.
- Participants may be on prednisone ≤10 mg/day at study entry. Prednisone may be increased as indicated after the end of the treatment period on Day 168 (- 7 days). At the investigator’s discretion, glucocorticoids may be tapered during the study.
- Any other less common DMARDs

The study team will make every attempt for the newly enrolled subjects to receive their COVID-19 vaccine booster from an outside vaccination clinic before randomization. In the event that an enrolled subject requires a vaccine booster during the treatment phase, the study team will make an accommodation of a 1-week interruption of the study drug. The subject will receive the vaccination at their preferred vaccination clinic.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from study intervention does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. Once enrolled, should study participant evidence a clinically significant finding, the PI or Medically Responsible Investigator will determine if any change in participant management is needed.

An investigator may discontinue study intervention in a participant for the following reasons:

- Completion of study intervention
- Disease progression which requires discontinuation of the study intervention
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Investigator discretion as in Sections 6.4, 6.5 and 7.2
- Positive pregnancy test
- Lymphocyte count less than 500 cells/mm3, confirmed by repeat testing
- ANC less than 500 cells/mm3, confirmed by repeat testing

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 14 days (+14 days) following the last dose of study therapy. Participants are free to withdraw consent at any time upon request. Participants may also choose to withdraw treatment but remain in the study for follow up. Participants must be withdrawn consistent with Section 6.1.2. Additionally, the PI or Medically Responsible Investigator may also choose to withdraw treatment or withdraw a participant from the study based on clinical or professional judgement. An investigator may withdraw treatment or a participant from study for the following reasons:

- Request by participant to be withdrawn from the study.
- Flares not resolving within 28 days or if, in the opinion of the medically-responsible investigator, the participant requires immediate immunosuppressive therapy that is not allowed in the protocol.
- Any Grade 4 adverse event that is unexpected and at least possibly related to study drug.
- More than 45 days delay in treatment after the screening visit.
- More than one (1) “no-show” for a visit.
- Persistent elevation of LFTs of > 2 times upper limit of normal persistently present on repeated samples 14 days +/- 7 days apart.

- >30% increase in serum creatinine from baseline at enrollment, persistently present on repeated samples 14 days +/- 7 days apart.
- Increase in proteinuria at the time of screening visit to protein to creatinine ratio of more than 1.000 mg/dL or more than 1000 mg in a 24 hours urine collection, persistently present on repeated samples 14 days +/- 7 days apart.
- Any other reason that, in the opinion of the responsible Investigator or Medically Responsible Physician, poses unacceptable risk to the participant.
- Infections requiring intravenous antibiotic treatment.
- Development of any malignancy.
- Urine BK virus level of more than 10 million copies/ml by quantitative PCR or detection of BK virus in serum by quantitative PCR.
- Non-compliance with treatment (<80% compliance by pill count).

The reason for participant discontinuation or withdrawal from the study will be recorded on the Voluntary Study Withdrawal Case Report Form (CRF). Participant who signs informed consent and are randomized, but do not receive the study drug, may be replaced.

Participants who sign informed consent, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn from the study, will be replaced.

A Participant is considered to have completed the study when he/she has completed 168 days of treatment with Tofacitinib and the day 196 follow-up assessments.

Participants randomized to a study arm who withdraw from the trial prior to starting on study drug will be replaced. Participants who withdraw study treatment and/or withdraw from the trial for any reason other than drug related adverse events after initiating the first dose of Tofacitinib and before completing 112 doses of Tofacitinib (study day 56) will also be replaced in order to maintain the sample size of 20 participants on Tofacitinib and 10 participants on placebo, for total of 30 evaluable participants. Based on experience with studies in SS participants, we expect a withdrawal rate of approximately 25% and therefore plan for a target enrollment of 30 participants plus 11 participants in event of participant withdrawal.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for two (2) scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 7 days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.

- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 STUDY ASSESSMENT AND PROCEDURE SCHEDULING

All the procedures and assessments explained below may be completed within the visit window period -45 days for the screening visit and +/- 7 days for follow up visits to accommodate scheduling and to reduce burden to participants (i.e., flexibility to optimize time in clinic to accommodate patient preferences).

8.1.1 STUDY PHASES

PRE-SCREENING VIA PROTOCOL: 15-D-0051

Participants will be pre-screened on the "Characterization of Diseases with Salivary Gland Involvement" protocol (15-D-0051). Those with mild-to-moderately active primary SS and no obvious exclusion criteria will be offered the chance to enroll in 20-D-0131.

NIH participants with SS who are identified from either Protocol 11-D-0172 or Protocol 15-D-0051 will be offered participation in the study if they are found to have mild to moderate disease activity and no obvious exclusion criteria. Pre-screening assessments will be done during routine clinical follow up or initial evaluations and will include review of medical history, physical examination and laboratory assessment and concomitant medications. All participants referred to this study will be enrolled to protocol 15-D-0051.

Screening Period (-45 days to Day 1):

Participants may be scheduled for screening visits at the NIH Dental clinic, NIH Outpatient 9 Clinic or the 5SWS Day Hospital. Screening procedures will be performed as part of this study. Any protocol mandated screening parameter greater than 30 days from screening visit must be repeated for the screening visit. Subjects will be asked to fast on the day of the appointment and to avoid taking saliva stimulants 24 hours prior to the appointment.

The following procedures will be done during the Screening Period:

- Informed Consent
- Review of inclusion and exclusion criteria
- Medical history and physical examination,
- Vital sign measurements,
- Dental history,
- Oral, and Head and Neck examinations,
- Saliva Collection
- Saliva Flow rates
- Salivary Gland Ultrasound,
- Comprehensive Ophthalmologic Exam
  - Vision exam
  - Intraocular pressure (IOP)
  - Dilated exam (fundoscopy)
  - Schirmer’s test with and without anesthesia

  - Ocular surface staining (Fluorescein, Lissamine green)
- EKG
- Concomitant medications review
- Minor Salivary Gland Biopsy. (If participants were previously seen on 15-D-0051 within the last twelve months and the appropriate minimum necessary tissues and research studies were procured, this biopsy may be used as the baseline biopsy).
- Assessment of SS activity: ESSDAI, PGA
- Laboratory studies:
  - Complete blood count with differential,
  - Serum chemistry panel (creatinine, glucose, urea nitrogen, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, albumin),
  - Pregnancy test (serum or urine; for females with reproductive potential only),
  - Urinalysis and random urine protein/creatinine ratio,
  - Lipid panel: LDH (low density lipoprotein), HDL (high density lipoprotein), TG (Triglycerides), Total cholesterol
  - Lipoprotein Profile: Apolipoprotein A-1, Apolipoprotein
  - ANA and anti-ENA panel (anti-RNP, anti-SmRNP, anti-SSA, anti-SSB), anticardiolipin antibodies, lupus anticoagulant, and anti-beta2-glycoprotein antibodies, anti-dsDNA antibodies,
  - Serum complement components C3 and C4
  - Quantitative Immunoglobulins: IgA, IgG, IgM
  - Serum protein electrophoresis (SPEP)
  - Screening serologies for hepatitis B, hepatitis C and HIV (per NIH lab each of these tests may only be done once within a six month period)
  - Tuberculosis screening using the QuantiFERON Gold test
  - Anti-varicella IgG
  - BK virus serum and urine quantitative PCR level
  - Cryoglobulins

After confirmation of eligibility, the PI or otherwise designated AI will contact the Clinical Center Research Pharmacy to randomize the Participant.

8.2 Efficacy Assessments

8.2.1 Clinical Evaluations

Clinical assessments will take place the Dental Clinic, Outpatient Clinic (OP), or 5SWS Day Hospital. Vascular assessments will be performed in the Vascular Lab of the CRC, Salivary assessments will be performed at the Salivary Disorders and Sjögren's syndrome Clinic at the Dental Clinic, Outpatient Clinic 1 (OP1). Subjects will be asked to fast on the day of the appointment and to avoid taking saliva stimulants 24 hours prior to the appointment.

Study Day 1/Visit 2 (on site visit):

- Concomitant medication review
- Drug Accountability- Dispense 35-day supply of study drug
- Vital sign assessments
- Presenting symptoms, abbreviated medical history, and physical examination
- Adverse event review

- Dental History and Oral and Head and Neck examination
- Salivary Collection
- Salivary flow rate
- Oral Microbiome
- Laboratory studies:
  - Complete blood count (CBC) with differential,
  - Serum chemistry panel (creatinine, glucose, urea nitrogen, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, albumin),
  - Pregnancy test (urine or serum; for females of reproductive potential only),
  - Urinalysis and random urine protein/creatinine ratio,
  - BK virus serum and urine quantitative PCR level,
  - Lipid panel: LDH (low density lipoprotein), HDL (high density lipoprotein), TG (Triglycerides), Total cholesterol,
  - Lipoprotein Profile (Apolipoprotein A-1, Apolipoprotein)
  - Lymphocyte pheno-TBNK,
  - Inflammatory markers (hs-CRP, ESR),
  - ANA and anti-ENA panel (anti-RNP, anti-SmRNP, anti-SSA, anti-SSB), anticardiolipin antibodies, lupus anticoagulant, and anti-beta2-glycoprotein antibodies, Anti-ds DNA antibodies,
  - Serum complement components C3 and C4,
  - Quantitative immunoglobulins (IgA, IgG, IgM),
  - Research Labs - 2 red SST, 6 red/green CPT, 1 PAX RNA);
  - Anti-SARS-CoV-2 antibodies
- Mechanistic studies: (intracellular signaling molecules, cytokine expression, circulating immune cell types and autoreactive B cells) – All samples will be run simultaneously for each assay at the end of the study
- Assessment of SS disease activity (ESSDAI, PGA)
- Vascular function studies:
  - Peripheral Wave Analysis (SphygmoCor)
  - Peripheral Arterial Tonometry (Endopat)
  - Cardio-ankle vascular index (CAVI)
- Patient questionnaires (ESSPRI, Dry Mouth Questionnaire, OHIP-14, Xerostomia VAS,FSS, PROMIS-57, SF-36, AECG Symptom Questionnaire)
- Study drug administration:
  - A 35-day supply of study drug or placebo will be dispensed to participants on study day 1 with instructions regarding twice daily dosing regimen and a review of potential side effects. No drug will be dispensed to a female participant of reproductive potential until negative pregnancy test results (serum or urine) have been obtained within 24 hours.

- For acute infection(s) requiring antibiotics discovered on Day 1: Any participant found to have an acute infection at baseline visit (Day 1 visit) will have the study drug withheld and their next visit will be scheduled for no more than 30 days later;
- Infections prior to 14 days of Day 1: study medication may be administered
- Between -14 to Day 1: study drug will be delayed up to the upper limit of 45 days from screen date
- If the above stated 14 days puts the patient beyond the limits of protocol mandated pre-screening interval, the participant will be excluded from study participation and then give the opportunity to be re-evaluated and re-enrolled.
- If the infection resolves, study medication will be started. If infection does not resolve within 30 days the participant will be removed from the study
- If a medically significant abnormal lab result (i.e., complete blood count, serum chemistries, pregnancy test, urinalysis and random urine protein/creatinine ratio) occurs at baseline (Day 1 visit), requiring repeat for confirmation, the study drug will be withheld and the next visit will be scheduled no more than 30 days later; if repeat testing reveals resolution of abnormal results, participants will be instructed to begin study medication. If the abnormal lab result does not resolve, participants will be removed from the study. Vascular function studies or research labs will not be repeated.

Study Days 7, 21, 42, 70, 154 (+/- 3 days) Telephone Calls

All participants will receive a telephone call from the study coordinator on study days 7, 21, 42, 70, and 154 (+/- 3 days). These calls will confirm study drug compliance, document any adverse events, and record any new or discontinued concomitant medications. A script with standardized questions will be used to confirm compliance with study drug.

Study Day 14/Visit 3: (on site visit)

All participants will return to the Clinical Center for study day 14 (+/- 7 days); they will be seen in either an outpatient clinic or Day Hospital. The following procedures will be performed at this visit:

- Adverse event assessment
- Concomitant medication review
- Vital sign measurements
- Presenting symptoms, abbreviated medical history and, physical examination
- Laboratory studies:
  - Complete blood count with differential,
  - Serum chemistry panel (creatinine, glucose, urea nitrogen, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, albumin),
  - Pregnancy test (urine or serum; for females of reproductive potential only),

- Urinalysis, random urine protein/creatinine ratio,
- BK virus serum and urine quantitative PCR level

Study Days 28 (Visit 4), 56 (Visit 5), 112(Visit 7), 140 (Visit 8) (on site visits):
All participants will return to the Clinical Center will be seen at the Dental clinic, Outpatient 9 Clinic, or the 5SWS Day Hospital on study days 28, 56,112,140 (all visits +/- 7 days) for a brief visit. Participants will be asked to bring study medication bottle to confirm study drug compliance as well as re-issued of a new 35 day drug supply. The following procedures will be performed at this visit:

- Adverse event assessment
- Concomitant medication review
- Drug accountability-Returning used drug bottle
- Drug accountability- Dispense 35-day supply of study drug
- Vital sign measurements
- Presenting symptoms, abbreviated medical history and physical examination
- Laboratory studies:
    - Complete blood count with differential,
    - Serum chemistry panel (creatinine, glucose, urea nitrogen, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, albumin),
    - Pregnancy test (urine or serum; for females of reproductive potential only),
    - Urinalysis, random urine protein/creatinine ratio
    - Serum complement components C3 and C4,
    - Quantitative immunoglobulins (IgA, IgG, IgM)
    - BK virus serum and urine quantitative PCR level
    - Inflammatory markers (ESR, CRP)
- Assessment of SS disease activity (ESSDAI, PGA)

Study Day 84/Visit 8 (on site visit):
All participants will be seen at the Dental clinic, Outpatient 9 Clinic or the 5SWS Day Hospital on study day 84 (+/- 7 days). They will be asked to bring study medication bottles to assess drug compliance as well as re-issued of a new 35 day study drug supply. Participants will be asked to fast after midnight the night prior for the fasting lipid profile and to avoid taking saliva stimulants 24 hours prior to the appointment. The following procedures will be performed at this visit:

- Adverse event assessment
- Concomitant medication review
- Drug accountability- Returning used drug bottle
- Drug accountability- Dispense 35-day supply of study drug
- Vital sign measurements
- Presenting symptoms, abbreviated medical history and physical examination
- Interim Dental History and Oral, and Head and Neck examination

- Ophthalmologic Exam
    - Vision exam,
    - Schirmer's test with/without anesthesia,
    - Ocular surface staining (Fluorescein, Lissamine green)
- Saliva Collection
- Salivary Flow Rate
- Laboratory studies:
    - Complete blood count with differential,
    - Serum chemistry panel (creatinine, glucose, urea nitrogen, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, albumin),
    - Pregnancy test (urine or serum; for females of reproductive potential only),
    - Urinalysis and random urine protein/creatinine ratio,
    - ANA and anti-ENA panel (anti-RNP, anti-SmRNP, anti-SSA, anti-SSB) anticardiolipin antibodies, lupus anticoagulant, and anti-beta2-glycoprotein antibodies, Anti-dsDNA antibodies,
    - Serum complement components C3 and C4
    - Quantitative Immunoglobulins, (IgA, IgG, IgM)
    - Serum protein electrophoresis (SPEP)
    - Inflammatory markers (ESR, CRP)
    - BK virus serum and urine quantitative PCR level
    - Lipid panel: LDH (low density lipoprotein), HDL (high density lipoprotein), TG (Triglycerides), Total cholesterol,
    - Lipoprotein Profile,
    - Lymphocyte pheno-TBNK,
    - Research Labs (2 red SST, 6 red/green CPT, 1 PAX RNA)
- Vascular function studies
    - Peripheral Wave Analysis (SphygmoCor)
    - Peripheral Arterial Tonometry (Endopat)
- Cardio-ankle vascular index (CAVI)Assessment of SS disease activity (ESSDAI, PGA)
- Patient questionnaires (ESSPRI, Dry Mouth Questionnaire, OHIP-14, Xerostomia VAS, FSS, PROMIS-57, SF-36, AECG Symptom Questionnaire)

Study Day 168/Visit 9 (end of treatment visit):
All participants will be seen at the Dental clinic, Outpatient 9 Clinic or the 5SWS Day Hospital on study day 168 (+/- 7 days). Study participants will be asked to return medication bottles to confirm compliance with study drug and to fast overnight for lab tests. Subjects will be asked to avoid taking saliva stimulants 24 hours prior to the appointment.

- Adverse event assessment
- Concomitant medication review
- Drug accountability-Returning used drug bottle
- Vital sign measurements
- Interim Dental History and Oral and Head and Neck examination
- Saliva Collection

- Salivary flow rate
- Oral Microbiome Collection
- Ophthalmologic Exam
  - Vision exam
  - Schirmer's test with/without anesthesia
  - Ocular surface staining (Fluorescein, Lissamine green)
  - Pentagraph for tear breakup time, redness scale, tear lake if available
  - MMP-9 simple strip test
- Minor Salivary Gland Biopsy
- Salivary Gland Ultrasound
- Presenting symptoms, abbreviated medical history and physical examination
- Laboratory studies:
  - Complete blood count with differential,
  - Serum chemistry panel (creatinine, glucose, urea nitrogen, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, albumin),
  - Pregnancy test (urine or serum; for females of reproductive potential only),
  - Urinalysis and random urine protein/creatinine ratio,
  - Inflammatory markers (CRP, ESR),
  - ANA and anti-ENA panel (anti-RNP, anti-SmRNP, anti-SSA, anti-SSB), anticardiolipin antibodies, lupus anticoagulant, and anti-beta2-glycoprotein antibodies, Anti-dsDNA antibodies,
  - Serum complement components C3 and C4
  - Quantitative Immunoglobulins, (IgA, IgG, IgM)
  - Serum protein electrophoresis (SPEP)
  - Lipid panel LDL (low density lipoprotein), HDL (high density lipoprotein), TG (triglycerides), total cholesterol
  - Lipoprotein Profile
  - Lymphocyte pheno-TBNK
  - BK virus serum and urine quantitative PCR level
  - Anti-SARS-CoV-2 Antibodies
  - Mechanistic studies: (intracellular signaling molecules, cytokine expression, circulating immune cell types and autoreactive B cells) – All samples will be run simultaneously for each assay at the end of the study
- Assessment of SS disease activity (ESSDAI, PGA, Salivary flow)
- Patient questionnaires (ESSPRI, Dry Mouth Questionnaire, OHIP-14, Xerostomia VAS, FSS, PROMIS-57, SF-36, AECG Symptom Questionnaire)
- EKG
- Assessment of biologic effect
- Assessment of durability of the clinical and biological effects

Study Day 196 (end of study visit):

All participants will be seen at the Dental clinic, Outpatient 9 Clinic or the 5SWS Day Hospital. They will be asked to bring their bottles of study drug to account for any remaining study drug at the end of study visit (+/- 7 days). Participants will be asked to fast after midnight the night prior for the fasting lipid profile. Subjects will be asked to avoid taking saliva stimulants 24 hours prior to the appointment. The following procedures will be performed at this visit:

- Adverse event assessment
- Concomitant medication review
- Vital sign measurements
- Interim Dental History and Oral, Head and Neck Exam
- Saliva Collection
- Saliva Flow rates
- Ophthalmologic Exam
  - Vision exam
  - Intraocular pressure (IOP)
  - Schirmer's test with/without anesthesia
  - Ocular surface staining (Fluorescein, Lissamine green)
  - Pentagraph for tear breakup time, redness scale, tear lake (if available)
- Presenting symptoms, abbreviated medical history, and physical examination
- Laboratory studies:
  - Complete blood count with differential,
  - Serum chemistry panel (creatinine, glucose, urea nitrogen, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase),
  - Pregnancy test (urine or serum; for females of reproductive potential only),
  - Urinalysis and random urine protein/creatinine ratio,
  - Inflammatory markers (CRP, ESR),
  - ANA and anti-ENA panel (anti-RNP, anti-SmRNP, anti-SSA, anti-SSB) anticardiolipin antibodies, lupus anticoagulant, and anti-beta2-glycoprotein antibodies, Anti-dsDNA antibodies,
  - Serum complement components C3 and C4
  - Quantitative Immunoglobulins, (IgA, IgG, IgM)
  - Serum protein electrophoresis (SPEP)Lipid panel LDL (low density lipoprotein), HDL (high density lipoprotein), TG (Triglycerides), total cholesterol
  - Lipoprotein Profile
  - Lymphocyte pheno-TBNK
  - BK virus serum and urine quantitative PCR level
  - Research Labs (2 red SST, 6 red/green CPT, 1 PAX RNA)
  - Mechanistic studies: (intracellular signaling molecules, cytokine expression, circulating immune cell types and autoreactive B cells) – All samples will be run

simultaneously for each assay at the end of the study
- EKG
- Assessment of SS disease activity (ESSDAI, PGA)
- Patient questionnaires (ESSPRI, Dry Mouth Questionnaire, OHIP-14, Xerostomia VAS, FSS, PROMIS-57, SF-36, AECG Symptom Questionnaire).
- Vascular function studies
  - Peripheral Wave Analysis (SphygmoCor)
  - Peripheral Arterial Tonometry (Endopat)
  - Cardio-ankle vascular index (CAVI)
- Assessment of biologic effect
- Assessment of durability of the clinical and biological effects

Unscheduled Visits:

In the event of an adverse event or other reason that results in an unscheduled visit and will take place at the Dental clinic, Outpatient 9 Clinic, the 5SWS Day Hospital. Clinically appropriate assessments from the list below will be completed at the discretion of the principal investigator and medically responsible investigator at this visit:

- Adverse event assessment (AE)
- Concomitant medication review
- Vital sign measurements
- Medical history and physical examination
- Laboratory studies
  - Complete blood count with differential,
  - Serum chemistry panel (creatinine, glucose, urea nitrogen, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase)
  - Pregnancy test (urine or serum; for females of reproductive potential only)
  - Urinalysis and random urine protein/creatinine ratio,
  - Inflammatory markers (CRP, ESR),
  - anti-ENA (Sm, RNP, SSA, SSB), serum complement components C3 and C4
  - Quantitative Immunoglobulins (IgA, IgG, IgM)
  - Serum protein electrophoresis (SPEP)
  - Lipid panel LDL (low density lipoprotein), HDL (high density lipoprotein), TG (Triglycerides), total cholesterol
  - Lipoprotein Profile
  - Lymphocyte pheno-TBNK
  - BK virus serum and urine quantitative PCR level
  - Research Labs (2 red SST, 6 red/green CPT, 1 PAX RNA)
- EKG
- Assessment of SS disease activity (ESSDAI, PGA)

- Patient questionnaires Patient questionnaires (ESSPRI, Dry Mouth Questionnaire, OHIP- 14, Xerostomia VAS, FSS, PROMIS-57, SF-36, AECG Symptom Questionnaire)
- Drug accountability

8.2.2 Follow-up/Termination Procedures:

While on this study, participants will continue to receive regular medical care from their primary physicians. Any AEs reported will be followed by the investigators as described in Section 16.1.8. Following completion of the study or after withdrawal from the study, participants will return to the care of their referring physicians. Participants may continue their follow up visits on protocol 15-D-0051 as appropriate. A summary of the participants' course in the study will be sent to the referring physician.

Participants who withdraw or are withdrawn from the study after receiving study treatment will be asked to complete the day 168 and 196 for close out safety assessments. Participants are deemed ineligible before study day 1 or randomization will resume care with their referring physician with no further evaluation in this protocol.

8.2.3 Duration of Study Participation

Study participation will be a maximum of 241 days, comprised of a 45 day screening period 168 days treatment period, and 28 day follow up period. All study time periods are inclusive of a window of +/- 7 days for study days 1, 28, 56, 84, 112, 140 , -7 days for study day 168and +/- 3 days for telephone calls to accommodate any potential variability in participant scheduling (see Schedule of Events).

8.2.4 Vital Signs Measurement

Vital signs measurements will include pulse rate, systolic and diastolic blood pressure, respiratory rate, and temperature. These measurements will be performed at all study visits and recorded on CRF.

8.2.5 Adverse event assessment

Adverse events will be assessed by reviewing the interim medical history, performing a physical evaluation, asking open-end question of how the participant's feeling and reviewing laboratory results at each visit, as well as part of the clinical monitoring telephone calls on study days 7, 21, 42, 70, and 154 (+/- 3 days) as per Section 5.1.2.. After completing screening assessments, any adverse event (AE) or serious adverse event (SAE) reported by a subject, whether or not study drug has been administered, will be recorded by the investigators. Any AE/SAE prior to dosing will be categorized as "Baseline" and any AE/SAE after dosing will be categorized as "treatment-emergent."

8.2.6 Assessment of Sjögren's disease activity

SS disease activity will be assessed with the following measures:

- Clinical Labs
- ESSDAI: This validated disease activity measure reflects clinical events that occurred within 28 days and includes physical findings and laboratory measures.
- Physician Global Assessment (PGA) assess global disease activity

8.2.7 Assessment of Changes in Exocrine Function

Changes in salivary flow will be assessed by measuring whole unstimulated saliva flow (WUS) and glandular parotid and submandibular/sublingual unstimulated and 0.2% citric acid stimulated flow rates.

Changes in lacrimal flow will be measured by Schirmer's test.

8.2.8 Assessment of changes in oral microbiota

Supragingival plaque oral microbiome will be collected from three sites on posterior teeth. Decayed, missing, filled teeth (DMFT) scores and periodontal charting will be procured at plaque collection.

8.2.9 Salivary Gland Ultrasound

An ultrasound of the salivary glands may be done in the SS clinic for research purposes. Changes in ultrasonographic findings will be assessed at baseline and at the study day 168. Salivary gland ultrasound can be used to assess the echogenicity and homogeneity of the salivary glands including the submandibular and parotid glands. Validated scoring criteria will be used to assess ultrasonographic feature parameters.

8.2.10 Participant questionnaires

The following assessments will be utilized to assess participant reported outcomes:

1. EULAR Sjögren's syndrome patient reported index (ESSPRI)
2. 2002 American-European Consensus Group (AECG) Criteria Subjective Symptoms
3. Patient Dry Mouth questionnaire
4. Xerostomia visual analog scale [VAS]
5. Fatigue as measured by FSS
6. PROMIS-57 Profile version 2.0
7. Quality of life by the Short Form 36 (SF36) questionnaire
8. Oral health related quality of life by the OHIP-14.

8.2.11 Clinical Laboratory Assessments

The CLIA certified clinical laboratories at the NIH Clinical Center (Department of Laboratory Medicine) will be the central laboratories for all routine clinical laboratory parameters. A serum or urine pregnancy test will be performed for female participants at screening, as per study efficacy evaluation measures, unless postmenopausal (no menstrual period for 2 years or more), had a previous hysterectomy or removal of the ovaries. Some of the testing may be performed at an outside commercial laboratory for patient convenience. Participants will be asked to complete safety visits and further follow-up will be done under the Pathogenesis and/or Natural History of Sjögren's syndrome Protocol (11-D-0172) and/or by their local physicians. Participants will have blood samples drawn through phlebotomy. The laboratory at the NIH Clinical Center will be the central laboratory for all clinical laboratory parameters. Routine testing for various viral infections, including hepatitis B and C and HIV, will be done, since these viruses have been shown to be a cause of salivary gland dysfunction. A positive test for any of these viruses will

affect healthy subjects' participation in this protocol (5.2). Additional testing for COVID-19 antibodies will be done, since Sjogren's Syndrome patients may be at greater risk for infection with COVID-19. Moreover, COVID-19 is now known to cause a plurality of post-infection complications including local effects on the mouth such as taste loss and dry mouth, as well as systemic affects including malaise, fatigue, and joint pain. These are also common clinical complaints in the study population. Participant's participation will not be affected by the results of these tests, but may be used to clinically contextualize interval changes in symptom severity (ESSDAI) in the event of symptomatic or asymptomatic (unknown) infection

8.3 LABORATORY RESEARCH STUDIES

8.3.1 Mechanistic studies

Mechanistic studies will be conducted to investigate effects of Tofacitinib on intracellular signaling molecules, cytokine expression, circulating immune cell types and autoreactive B cells. Results of these mechanistic studies will be used to compare responses in participants on Tofacitinib versus placebo.

All samples for the mechanistic assays will be collected at baseline or study day 1, prior to treatment, and study days 84, 168, and 196. For unscheduled visits, samples for mechanistic studies may be collected when possible. These assays will be performed in laboratories at the NIH. However, all samples will be processed for immediate use or cryopreserved and stored in freezers located in Building 10 (1N). To reduce confounding from variability between multiple assays, all of the samples will be treated appropriately, frozen and stored until all samples can be run simultaneously, for each assay, at the end of the study.

The following is a list of the planned mechanistic studies:

- Change in inflammation in the MSG (i.e., focus score), numbers of infiltrating lymphocytes, and the immunophenotypic distribution in the tissues using immunohistochemistry, flow cytometry, and (when tissue is available) single cells RNA sequencing.
- Changes in levels of SS-related autoantibodies (e.g., anti-Ro52, -Ro60, -la, -CCP, -Sm, -TRIM38, -IFN, and others) using LIPS;
- Ligand-induced STAT phosphorylation in circulating T cells and monocytes using phosphoflow assessment of single cells;
- Expression of STAT-related target genes; expression of pro-inflammatory and immunoregulatory cytokines in T cells and monocytes using RNAseq;
- RNA sequencing of MSG to detect dominant pathway alterations including, but not limited to inflammatory (e.g., "interferon signature", "granulocyte signature") and secretory pathways.
- RNAseq in PBMCs to detect dominant pathway alterations including, but not limited to inflammatory pathways (like "interferon signature", "granulocyte signature"); measures of CD3+ T cell expression of IFN regulatory factor-related genes using RNAseq;

- Alteration in peripheral blood immune cell populations with special attention to CD4+, CD25+, Foxp3+ regulatory subsets, and Th17 cells.
- Measures of serum cytokines (IL-2, 4, 6, 7, 9,12, 15, 17, 23, TNFa, TNFb, IFNα and IFNγ);
- Measurement of cholesterol efflux capacity and NMR lipoprotein profile (particle size and number) and insulin resistance.
- Changes in vascular function, as assessed by the reactive hyperemia index (RHI) using Endopat device, and arterial stiffness using cardio-ankle vascular index (CAVI). Both are surrogate markers of vascular damage and future atherosclerosis development which are amenable to change within this duration of treatment.

Additional biomarker studies: Unused biological samples from above (e.g., whole blood, plasma, serum, and saliva) from the planned mechanistic studies will be frozen and stored for future use. Consent for storage is addressed in informed consent document.

8.4 BIOSPECIMEN EVALUATIONS

Research samples will be collected and stored in locked secure freezers in Building 10 and Building 50 on the NIH campus. Only study investigators and participating research personnel will have access to the samples. Samples will be kept indefinitely unless there is a significant justification for destroying them. The PI will report the loss or destruction of samples collected under this protocol to the Institutional Review Board (IRB).

All samples will be coded and will not have personal identifiers. The codes for identifiers will be contained in a secure, password protected, electronic database (Clinical Trials Data Base (CTDB)) and a participant identification log will be maintained in secure research files maintained in secure and locked offices of the research team...

Coded samples may be shared with collaborators within and outside the NIH. Any remaining samples will be stored in the NIDCR or NIAMS locked freezers. Stored samples may be used for studies related to SS or other autoimmune or disorders affecting salivary glands. Approval from the IRB will be obtained prior to any research use of stored samples beyond the scope of this study.

All participant samples will be coded and used for research purposes without sharing identifying information. This information will be stored on password protected computers.

8.4.1 Correlative Studies for Research/Pharmacokinetic Studies: N/A

8.4.2 Samples for Genetic Analysis

Tissues to be collected for possible genetic analyses include: whole blood and/or PBMCs, and minor salivary gland tissues.

Description of the scope of genetic/genomic analysis

These studies may include, but are not limited to, RNA sequencing, epigenetic sequencing analyses, and whole genome sequencing. Specifically, we may conduct the following sequencing analyses:

RNA sequencing (pending tissue availability):

- Bulk RNA sequencing of peripheral blood mononuclear cells and minor salivary glands.
- Single cell, single nuclei, or spatial-transcriptomics RNA sequencing of minor salivary glands and peripheral blood mononuclear cells.

Epigenetic sequencing analyses (pending tissue availability):

- ATAC-Sequencing or other epigenetic sequencing techniques on peripheral blood mononuclear cells and minor salivary glands

Whole genome sequencing (WGS):

- WGS of minor salivary gland or peripheral blood mononuclear cells.

Description of how privacy and confidentiality of medical information/biological samples will be maximized

As part of this study, certain genetic studies, such as whole genome, exome, whole transcriptomic, or epigenomic sequencing may be utilized to understand the effect of Tofacitinib in SS. These studies will not be completed until after data lock. Genetic material (DNA, RNA) will be extracted from PBMCs or tissues and used for sequencing (DNA whole genome, RNA whole transcriptome, or other sequencing methodologies). The samples will be de-identified and coded in a password protected database. Data linking individual sequencing results with individual patients will be available to only the PI and co-investigators. De-identified sequencing data may be shared with collaborators through approved NIDCR Data Transfer Agreements (DTA). Genetic material will not be used for other specific but unrelated investigations unless permission is first granted by the NIH IRB as well as the subject.

The expression profile of mRNA and non-coding RNAs may be analyzed from various tissues and body fluids, such as whole blood, blood components, saliva, urine and biopsy samples (e.g., salivary gland biopsies).

NIH's policy for data-sharing for federally funded genome-wide association studies requires that genotypic and phenotypic information from such studies will be made available through the NIH GWAS data repository designated as database of Genotypes and Phenotypes (dbGAP). Only coded de-identified data will be submitted to dbGAP. The data include the results of the GWAS and selected demographic and clinical variables. We anticipate that similar requirements may be put in place in the future for whole genome sequencing/whole transcriptome data, too.

Medical information and biological samples relating to genomic material will follow the same protections as other biospecimens and medical information collected in this study and as outlined in sections 8.4 Biospecim**ens**, 10.1.5 Confidentiality and Privacy and 10.2 Future Use of Stored Specimens and Data. Data related to genomic analysis will be shared in accordance with NIH

Genomic Data Sharing Policy as described in in section, 10.9.2, Genomic Data Sharing Plan. Whole genome association studies (GWAS), whole genome sequencing, RNA sequencing, and data deposition into dbGaP.

Management of Results

It is not expected that any of the genomic testing would result in a clinically actionable gene variant. The data obtained will be handled with confidentiality. However, if mutation(s) is/are found that seem to cause or contribute to the disease or phenotype under study, we will verify the

finding in a CLIA-certified laboratory. After consultation with the IRB the subjects will be informed and instructed that these genetic findings may require further analysis. A medical genetic counselor will be utilized as appropriate to communicate the genetic findings to the subjects.

It is conceivable that during traditional genetic studies we identify genes associated with Sjögren's syndrome which are also associated with other disorders unrelated to Sjögren's syndrome. This information will not be placed in the medical records, nor will it be discussed with subjects unless there is clear scientific evidence that this finding will have a clinically significant impact on the subject's prognosis or treatment. Sequencing may also identify variant genes that increase the subject's risk for other diseases or may have an impact on the prognosis of other diseases. The PI of this protocol (or his/her staff clinician, nurse, or genetic counselor) will be responsible for communicating that result to the participant. It is essential that this communication include a clear message that the absence of such a finding does not confidently exclude the presence of such a mutation and that if there is an indication for specific testing for any of the genes or disorders covered by current ACMGG secondary findings standards.

We will make no attempts to identify any of these variants and will not inform the subjects unless such variants are identified in our association studies of Sjögren's syndrome and there is clear scientific evidence that this finding will have a clinically significant impact on the subject's prognosis or treatment. In that case, we will contact all subjects and inform them that we have identified such a genetic variant in our cohort and ask them if they want to be informed about their individual result. Then, we will provide the data and appropriate counseling to the subjects who wish to be informed. The details of this process (such as the letter to the subjects) will be submitted to the IRB for approval. Since this is an evolving field, it is possible that we will identify sequence variants associated with Sjögren's syndrome, which may have an effect on the subject's treatment and or prognosis but for which there is no consensus in the medical community. In these cases, we will seek guidance from experts in the field (geneticists, ethicists and the appropriate subspecialists) and will provide a plan of action to the IRB based on their recommendations.

8.5 Safety and Other Assessments

Patient safety will be assessed through clinical assessments and laboratory studies during scheduled follow up visits (SOA), symptom assessment during interim phone calls (SOA), and assessment of AEs.

8.6 Adverse Events and Serious Adverse Events

8.6.1 Definition of Adverse Event

Adverse events (AE) are any unfavorable and/or unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome, or disease that occurs during the study, having been either absent at baseline, or if present at baseline, appears to worsen.

Events will be reported as AE's as described in section 8.2.5.

All AEs will be graded for intensity (severity) according to CTCAE version 5.0 and relationship to study drug as described below.

8.6.2 Definition of Serious Adverse Events (SAEs)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator, sponsor, or Pfizer, it results in any of the following outcomes:

- Results in death
- A life-threatening adverse event, (defined as a participant at immediate risk of death at the time of the event; it does not apply to an AE which hypothetically might have caused the death if it were more severe),
- Requires or prolongs hospitalization (i.e. the AE required at least a 24-hour inpatient hospitalization or prolonged a hospitalization beyond the expected length of stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion),
- Results in a congenital anomaly or birth defect (i.e., an adverse outcome in a child or fetus of a Participant exposed to the trial drug prior to conception or during pregnancy),
- Causes a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- Any other condition that, in the judgment of the investigator, represents a significant hazard or does not meet any of the above serious criteria but may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.6.3 Medical Events Not Qualifying as Adverse Events or Serious Adverse Events:

Signs and symptoms of pre-existing medical conditions will not be recorded or reported as AEs or SAEs, unless they represent a clinically significant change from the baseline disease status documented at the Pre-screening Visit. In addition, hospitalization for elective procedures or surgeries will not be considered SAEs, nor will inpatient hospitalizations for convenience.

8.6.4 Clinical Laboratory Test Results Not Qualifying as Adverse Events or Serious Adverse Events:

A clinically significant laboratory result that is present at baseline and does not change significantly during the study will not be reported as an AE or SAE. The clinical significance of a change in a laboratory result will be determined by the PI or medically responsible medical investigator.

The PI, along with the medically responsible investigator will evaluate all clinical laboratory and imaging results for clinically significant abnormalities and document the evaluation in the medical record and case report form. A clinically significant laboratory abnormality will be documented as an adverse event using the following criteria:

The abnormality,

- is not already encompassed by a reported adverse event (e.g., elevated AST need not be reported as an AE if Liver Failure has already been reported as an AE).

- is considered clinically significant by the Investigator.
- necessitates study drug dosing modification (i.e., dose reduction, interruption or discontinuation); and/or
- requires a therapeutic intervention (e.g., concomitant medication, blood transfusion or dialysis); and
- is unexplainable by the participant's current and past medical conditions
- is related to a SS flare.
    - A SS flare is any significant worsening of the signs, symptoms, and laboratory test abnormalities associated with SS. Any increase in the ESSDAI index of >3 or more will be considered as a SS flare[59].

8.7 Classification of an Adverse Event

8.7.1 Severity of Event

The intensity (severity) of AEs and SAEs will be graded according to a descriptive scale based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0

8.7.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the investigator who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

For all AEs and SAEs, the investigator will provide his best estimate of the causal relationship between the event and study drug, and the causal relationship between the event and study procedures. The degree of certainty about causality will be graded according to the following criteria.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related"

soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.7.3 Expectedness

For reporting purposes, the medically responsible investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Unexpected adverse events are those not listed in the Package Insert (P.I.) or Physicians' Desk Reference (PDR), published medical literature, protocol, informed consent document or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or PDR. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

For consistency of labeling and categorizing adverse events, the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 will be used in this study.

8.7.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

The severity of an AE will be documented at its highest level of severity. AEs characterized as intermittent require documentation of onset and duration of each episode.

Any time after informed consent is obtained, AEs and SAEs will be recorded and reported until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation.

8.8 ADVERSE EVENT REPORTING

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF) and will be reported to the IRB according to the NIH-OHSRP Policy 801: *Reporting Research Events*. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

8.8.1 Serious Adverse Event Reporting

Serious Adverse Events will be reported to:

- The NIH IRB according to NIH-OHSRP Policy 801: Reporting Research Events and Policy 802: Non-Compliance in Human Participants Research NIH-OHSRP Policy 801: Reporting Research Events and Policy 802: Non-Compliance in Human Participants Research, NIDCR Clinical Director's Office within 7 calendar days based on *NIDCR DIR Reporting* guidance.
- Pfizer Safety within twenty-four (24) hours of Institution's first awareness of an SAE, or immediately upon Institution's awareness if the SAE is fatal or life-threatening, according to Pfizer guidance and instructional material and templates. The study investigator will report to the Pfizer any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to Pfizer.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by Pfizer, if applicable and should be provided as soon as possible.

8.8.2 .Events of Special Interest

The following instances will be reported to Pfizer Safety as SAEs:

- Exposure to the Pfizer Product during pregnancy (see section 8.8.3) or lactation
- Drug overdose
- Medication error
- Occupational exposure to the Pfizer Product and
- Lack of effect of the Pfizer Product

- Potential drug-induced liver injury as assessed by if a Study subject develops abnormal values in aspartate transaminase ("AST") or alanine transaminase ("ALT") or both, concurrent with abnormal elevations in total bilirubin and no other known cause of liver injury, that event would be classified as a Hy's Law Case.

8.8.3 Reporting of Pregnancy

This study includes pregnancy information as safety data and pregnancies will be recorded if they begin any time after enrollment. Information about any pregnancy should be reported promptly as SAE's to Pfizer within 24 hours of the Institution becoming aware of the pregnancy according to Pfizer guidance and instruction and to the NIDCR Office of Clinical Director (OCD) within 7 working days; the DSMC will not receive an expedited report. All pregnancies identified during the study must be followed to conclusion and the outcome of each must be reported. The investigator should be informed immediately of any pregnancy in a study participant or a partner of a study participant. A pregnant participant should be instructed to stop taking study medication. The investigator should counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Tofacitinib has a pregnancy risk factor Category C; there are no adequate and well controlled studies in pregnant women. Pregnancy outcome should be determined and submitted to Pfizer Safety and the NIDCR, Office of Clinical Director. When possible, similar information should be obtained for a pregnancy occurring in a partner of a study participant. Should the pregnancy result in a congenital abnormality or birth defect Pfizer Safety and the NIDCR, Office of Clinical Director should be notified.

Sexually active participants with a partner able to become pregnant, will also be advised their partner should not become pregnant during study participation and 3 months following study completion. Participants and partners must agree to use effective birth control to be considered for study participation. The principal investigator or the medically responsible investigator will include discussion with participants or partners considering pregnancy after study participation during initial study participation discussions.

8.8.4 Unanticipated Problems (UP)

Definition of Unanticipated Problems (UP)

Any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; and
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others (which many include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or expected.

8.8.5 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the NIH Institutional Review Board (IRB) as per Policy 801.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESIS

All analyses in this trial are descriptive and exploratory in nature. No formal statistical inferences are planned.

- Primary Endpoint(s): The primary objective is to evaluate the safety and tolerance of Tofacitinib in participants with SS. The primary endpoints include number and rates of adverse events (serious adverse events, Grade 3 and 4 toxicities not fulfilling the criteria for SAE, and non-serious adverse events) and number and rates of SS disease flares.
- Secondary Endpoint(s): Secondary endpoints will be analyzed by comparisons between the treatment (all SS participants receiving Tofacitinib) and placebo groups once the last participant completes the 28 weeks (196 days).
- Exploratory Endpoint(s):

For the following exploratory endpoints, all changes will be assessed between baseline and end of treatment, unless otherwise specified.

- Changes in salivary glands as assessed by histopathology including focus score, inflammation quantification and immunophenotyping of infiltrates
- Global transcriptomic changes in peripheral blood monocytes and minor salivary glands with specific interrogation of IFN regulated genes and other inflammatory pathways using software tools like Ingenuity Pathway Analysis.
- Differences between the treatment/placebo groups in changes in individual disease activity measures (ESSDAI, PGA, tear production, salivary flow) at the end of Study Day 168 will be analyzed as repeated measures with change from baseline as the dependent variable.
- Changes in participant reported outcomes such as: ESSPRI, SF-36, FSS, PROMIS
- Changes in non-invasive vascular studies
- A change will be analyzed using the appropriate statistical test per each type of data collected between baseline and at Day 168.

9.1.1 SAMPLE SIZE DETERMINATION

This is a pilot, Phase Ib-IIa study intended to study predominantly the tolerability/toxicity of Tofacitinib. The number of participants for this study is arbitrary and is based primarily on the conventional numbers in Phase II studies and our experience with similar studies conducted previously. The primary endpoint is safety and tolerability. 15- 20 participants are commonly used as the sample size for open label safety studies. Our plan to have 20 Participants dosed with Tofacitinib to evaluate for safety and a placebo group of additional 10 participants for comparison is consistent with Phase I studies.

9.2 POPULATIONS FOR ANALYSES

9.2.1 Safety Population

All participants who receive at least one dose or part of a dose of the study intervention and complete a safety follow-up, whether withdrawn prematurely or not, will be included in the safety population. All data relating to safety will be listed and summarized separately for the treatment period and for the entire study. All safety reports will be reviewed by the Principal Investigator.

9.2.2 Intent to Treat Population

Anyone randomized and receiving at least one dose of study drug will be included in the intent to treat population.

9.2.3 Toxicity Evaluation

All participants will be evaluable for toxicity from the time of their first dose of study drug, Tofacitinib 5 mg, orally, twice daily.

9.3 STATISTICAL ANALYSES

9.3.1 General Approach

Demographics and clinical variables will be summarized by treatment group for each study visit. For continuous variables, descriptive statistics includes mean, standard deviation, median, and range. For categorical variables, counts and percentages will be reported. Due to exploratory nature of this study, statistical testing will be performed at the two-sided 5% level for the efficacy variables. The 95% confidence interval will be provided as well.

9.3.2 Analysis of the Primary Endpoints

The primary goal is to evaluate the safety and tolerance of Tofacitinib in participants with SS. For the safety population, the number and percentage of subjects with any AE, any related AE, any SAE, any Grade 3 and 4 toxicities not fulfilling the criteria for SAE, and non-serious adverse events and SS disease flares, as well as the total number of events for each category will be summarized by treatment group. AE's/SAE's will be reported from the time of consent. Events that are reported prior to the first treatment will be considered non-treatment emergent in analyses.

9.3.3 Analysis of the Secondary Endpoint(s)

Secondary endpoints listed in Section 3.0 will be analyzed for the ITT population. Continuous endpoints (e.g. change from baseline (Day 1) to end of treatment (Day 168) will be compared between treatments using analysis of covariance (ANCOVA) model with baseline as a covariate if normality assumption holds. Otherwise, the nonparametric alternative will be adopted. For repeated measures, linear mixed models will be used. For multi-omics data, transcriptional pathway analysis, graphical data visualization (heat maps, cluster analysis), and differential gene expression analysis will be performed.

Secondary endpoints will be analyzed by comparisons between the treatment (all SS participants receiving Tofacitinib) and placebo groups once the last participant completes the 28 weeks (196 days) of study.

- Change in the ESSDAI score between baseline and Day 168 (end of treatment).
- Change in the Physician's Global Assessment (PGA) scores between baseline and study day 168 (end of treatment).

9.3.4 Safety Analyses

The primary endpoint of this study is safety. Please refer to 9.2.2.

9.3.5 Baseline Descriptive Statistics

See 9.2.1 General Approach.

9.3.6 Exploratory Analyses

Exploratory endpoints are listed in Section 3.0 and analyses are listed in 9.2.1 General Approach.

10 REGULATORY AND OPERATIONAL CONSIDERATIONS

10.1 Informed Consent Process

10.1.1 Consent/Assent Procedures and Documentation

The principles of informed consent obtained by IRB authorized study team members will be in compliance with all IRB requirements. Informed consent will be completed prior to initiation of any study activities. All participants will receive an IRB approved and current consent form containing the purposes, procedures, benefits, and potential hazards of the study. This information will be reviewed with participant by either the principal or a qualified associate investigator. All prospective participants will be given ample time to read the consent form, and ask questions, before signing.

Individual potential participants are required to sign an informed consent document. The original forms will become part of the permanent medical record and kept on file in the participant's medical record, available for inspection by study monitors, auditors, and regulatory authorities, both federal and institutional. Copies will be provided to participants and a copy will be filed in participant's research records. As per regulatory and IRB requirement, informed consent documentation note will be placed in the individual participant electronic record, Clinical Research Information System (CRIS) documenting consent and process used to obtain consent.

The PI will be responsible to ensure that informed consent is obtained in accordance with the relevant Federal regulations and NIH Policy 301. The informed consent will be obtained by the PI or designated investigators that have taken NIMH informed consent course.

All the relevant research information necessary to make an informed decision will be disclosed to the prospective participants. The IRB approved research team member obtaining informed consent is responsible for assuring all potential participant questions have been appropriately answered and the potential participant comprehends information discussed. The individual obtaining the informed consent will make every effort to minimize any possibility of therapeutic misconception.

Consent for NIH staff will be obtained as detailed above with following additional protections:

Consent from staff members will be obtained by an individual independent of the staff member's team whenever possible. Otherwise, the consent procedure will be independently monitored by

the CC Department of Bioethics Consultation Service in order to minimize the risk of undue pressure on the staff member.

10.1.2 Telephone, Remote, and Electronic Consent

The informed consent document will be provided well in advance as a physical or electronic document to the participant or consent designee as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomfort and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to any research activities taking place.

Informed consent may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including NIH HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed. If the consent process is occurring remotely, participants and investigators will view individual copies of the approved consent document on screens at their respective locations; the same screen may be used when both the investigator and the participant are co-located but this is not required.

For telephone consent: When the research team study member is satisfied that the potential participant has been given an opportunity to ask questions and all questions have been satisfactorily answered the potential participant will sign and date the informed consent, with the actual date of consent. The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was returned. A fully executed copy will be sent to medical records and filed in the participant's medical records; a copy will be filed in the research records and a final copy will be returned via mail for the participant's records. Consent documentation will be entered in CRIS with a progress note to the individual participant medical record.

For electronic consent: The study team will confirm with the subject that they are comfortable using the electronic consenting before proceeding with obtaining consent. If not, other methods will be utilized. When an electronic document with a digital signature is used for the documentation of consent, this study will use the iMedConsent™ platform which is 21 CFR, Part 11 compliant to obtain the required signatures. During the consent process, participants and investigators will view the same approved consent document simultaneously in their respective locations. The identity of the participant will be determined by verifying a government issued identification card via the telehealth platform, prior to obtaining the signature. Electronic signature with a timestamp will be provided by required parties through system prompts. Once the completed consent has been saved, it will post to CRIS within a few minutes. All consents completed in iMedConsent™ will post to both the Documents tab and the Consents tab in CRIS. If the research participant has a FollowMyHealth™ account a copy of the completed consent will be posted to

their account within two business days. The study team will provide the research participant with a printed copy of the signed document.

10.1.3 Consent of Subjects who are, or become, decisionally impaired

Adults unable to give consent are excluded from enrolling in the protocol. Adults presenting with representative with legally authorized representation (LAR) documentation will also be excluded from study participation

10.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the Institutional Review Board (IRB), and Pfizer to provide the reason(s) for the termination or suspension. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, Pfizer, NIDCR Division of Intramural Research Data and Safety Monitoring Committee (DSMC), and regulatory authorities. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Institute DSMC and/or IRB.

10.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the Institute and its designees. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Institute and Pfizer.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Institute, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study.

The clinical study site will permit access to such records.

The study participant’s contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or Pfizer requirements.

Study participant research data will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NIDCR.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.4 Telehealth and Telemedicine

During extreme situations when travel to the NIH CC may not be feasible or advisable (e.g., inclement weather, pandemics), telehealth visits may be utilized to include follow-up and unscheduled visits.

ThinkAndor® will be utilized for the conduct of synchronous telehealth/telemedicine visits between NIH healthcare providers and their patients. The provider will document all clinically relevant information collected during the patient encounter in CRIS, just as they do for an onsite visit, and note in the documentation that the encounter occurred via telehealth/telemedicine. Obtaining remote consent via telehealth is explained in 10.1.2.

10.5 Outpatient/Outside Clinical Laboratory Testing

Outpatient/Outside Clinical Laboratory Testing may be performed by local CLIA-certified laboratories for study visits for non-local participants that are unable to have laboratory testing performed at the NIH. Participants will be given a laboratory order by the NIH heath team to be used at their local CLIA-certified laboratory. Participants and the CLIA-certified lab will be instructed to have lab results sent to NIH via fax within 7 business days (± 7 days) to the research team. Additional outpatient blood or urine tests may be ordered as clinically indicated. Lab work to be obtained at local CLIA-certified lab will follow required protocol visit labs.

Blood specimens for research assays will not be performed by outside laboratories. For remotely completed safety labs NOT covered by the patient's insurance, we will cover the cost for commercial laboratory testing.

10.6 Future use of Stored Specimens and Data

Research samples collected from participants consenting to this protocol will be stored in locked secure freezers belonging to NIDCR and NIAMS. The freezers are located in Building 10 and Building 50 at the NIH. Only study investigators and participating research personnel will have access to the samples. Samples will be kept indefinitely unless there is a significant justification for destroying them. The Principal Investigator will report the loss or destruction of samples collected under this protocol to the Institutional Review Board (IRB).

All samples will be coded and will not have personal identifiers. The codes for identifiers will be contained in a secure electronic database (CTDB) and a participant code log that is maintained in secure research files. An electronic record log with identifiers of all collected research specimens will be kept. These will be stored in secure NIH computers.

Coded samples may be shared with collaborators within and outside the NIH. Any remaining samples will be stored in the NIDCR or NIAMS locked freezers. Stored samples may be used for studies related to SS or other autoimmune or disorders affecting salivary glands. Approval from the IRB will be obtained prior to any research use of stored samples beyond the scope of this study.

All participant samples will be coded and used for research purposes without sharing identifying information and all collaborators will follow federal rules for clinical research.

10.7 Safety Oversight

In addition to the PI's responsibility for oversight, this study will be monitored by the NIDCR Division of Intramural Research Data and Safety Monitoring Committee (DSMC). The DSMC will include members with expertise in a broad range of areas, including, but not limited to, human subjects' protection, clinical trial implementation, biostatistics, rheumatology, and medical bone and mineral metabolism. The DSMC will meet periodically to assess safety and efficacy data (if applicable), study progress, and data integrity for the study. The DSMC will determine frequency of review at the first meeting, but typically will meet at least once a year. The DSMC may also choose to electronically review periodic data and safety reports in addition to convening data review meetings. If safety concerns arise, more frequent meetings may be held. In addition, unscheduled meetings can be requested by any party with responsibility of overseeing the study. The DSMC will provide recommendations to the NIDCR concerning the continuation, modification, or termination of the trial. The DSMC will operate under the rules of an NIDCR-approved charter. The roles and responsibilities of committee members and meeting procedures will be formally described in the charter.

The DSMC will provide its input to the National Institute of Dental and Craniofacial Research, Clinical Director and the PI.

The DSMC will be alerted if any of the following situations occur:

- An unexpected fatal or life-threatening event assessed as related to the use of study drug.
- Three or more participants with similar severe AEs (Grade 3 or 4) assessed as related to the use of study drug.

The Principal Investigator will be responsible for monitoring the accruing safety data related to suspension guidelines and for alerting the DSMC chair when a criterion is met. The DSMC chair, through the DSMC Executive Secretary, will be alerted by email within 7 calendar days of determination that a criterion has been met. The DSMC will issue a recommendation on study continuation to the NIDCR Clinical Director or designee after reviewing data related to the suspension guideline. If the study is stopped, participants will receive conventional care for any study-related AEs and continue to be followed for clinical and safety outcomes. Otherwise, the study will continue per the DSMC recommendations. The Principal Investigator and the Clinical Director will provide the recommendations of the DSMC to the IRB.

10.8 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by the NIDCR Clinical Research Operations and Management Support (CROMS) contractor. The monitor will evaluate study processes and documentation based on the International Council for Harmonization (ICH), E6: Good Clinical Practice guidelines (GCP).

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP). The CMP will specify the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of participant data to be reviewed), and the distribution of monitoring reports. Some monitoring activities may be performed remotely, while others will take place at the study site(s). Staff from the NIDCR CROMS contractor will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the CMP. Documentation of monitoring activities and findings will be provided to the study PI, NIDCR-OCTOM, and NIDCR Office of the Clinical Director (OCD) staff.

10.9 Quality Assurance and Quality Control

Internal quality assurance activities will include study team meetings, where the protocol team will review any new consents, unanticipated problems, and adverse events, and quarterly reporting of quality assurance/quality improvement activities to the NIDCR Office of the Clinical Director Clinical Operations Manager and NIDCR-OCTOM.

The study team will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

The data will be further validated via a series of manual edit checks, and all relevant data queries will be raised and resolved on an ongoing basis. Complete, clean data will be frozen to prevent further inadvertent modifications. All discrepancies will be reviewed and any resulting queries will be resolved with the investigators and amended in the database. All elements of data entry (i.e., time, date, verbatim text, and the person performing the data entry) will be recorded in an electronic audit trail to allow all data changes in the database to be monitored and maintained in accordance with federal regulations.

10.10 Data Handling and Record Keeping

10.10.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Clinical Trials Data Base (CTDB), a 21 CFR Part 11-compliant data capture system provided by the Research Nurse Coordinator. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Study staff will complete electronic case report forms (eCRFs) via a web-based electronic data capture (EDC) system (Clinical Trials Database, CTDB) that is compliant with Part 11 Title 21 of the Code of Federal Regulations. Participant electronic medical records in the Clinical Research Information System (CRIS) will be used as source documents for these eCRFs.

Participants will also complete periodic questionnaires as outlined in the study procedures through the Clinical Trial Survey System (CTSS) – an ancillary web-based application associated with CTDB. These participant-completed questionnaires in CTSS will be used as source documents for the study. The CTSS is accessible outside the NIH and allows participants to remotely respond to clinical questionnaires with secure passwords administered by CTDB. Security of the database system is maintained through an application firewall, military grade encryption and SSL certificates, removal of personal identifiers consistent with HIPAA requirements (45 C.F.R.164.514(a),(b)&(c)), and the incorporation of audit trails. The servers are physically located in a secured NIH data center with controlled limited access. If for any reason, the CTSS system is unavailable for use by a participant, questionnaires may be completed in paper form. The paper form will be used as the source. Study team member(s) will enter data into the CTDB database.

Paper-based CRFs and physician assessments may be completed in addition to completion of web-based CRFs. Completed paper-based forms will be imputed into appropriate CTDB database. CRFs, participant questionnaire data will be kept in the CTDB database.

Research records and all source documents will be kept in locked cabinets or rooms, and computer research databases will be stored in a secure, password-protected environment, per standard NIH policies. Only study investigators and participating research personnel will have access to the data.

In the future, other investigators (at the NIH) may wish to study these samples and/or data. In that case, IRB approval must be sought prior to any sharing of samples. Any clinical information shared about the sample without participant identifiers would similarly require prior IRB approval.

The research use of stored, unlinked or unidentified samples may be exempt from the need for prospective IRB review and approval. Exemption requests will be submitted in writing to the NIH Office of Human Participants Research, which is authorized to determine whether a research activity is exempt.

10.10.2 Study Records Retention

Study documents should be retained for a minimum of 3 years after the last approval of a marketing application in an International Council on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention, or as per the NIH Intramural Records Retention schedule. No records will be destroyed without the written consent of Pfizer Incorporated, if applicable. It is the responsibility of the Pfizer, to inform the investigator when these documents no longer need to be retained.

10.11 PROTOCOL DEVIATIONS AND NON-COMPLIANCE

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations to the NIH Institutional Review Board as per Policy 801.

Deviations must be addressed in study source documents and reported to NIDCR Office of Clinical Director. The investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.11.1 NIH Definition of Protocol Deviation

A protocol deviation is any changed, divergence, or departure from the IRB-approved research protocol.

- Major deviations: Deviations from the IRB approved protocol that have, or may have the potential to, negatively impact the rights, welfare or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.
- Minor deviations: Deviations that do not have the potential to negatively impact the rights, safety or welfare of subjects or others, or the scientific integrity or validity of the study.

10.12 PUBLICATION AND DATA SHARING POLICY

10.12.1 Human Data Sharing Plan

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer- reviewed journals.

10.12.2 Genomic Data Sharing Plan

This study will be conducted in accordance with the National Institutes of Health (NIH) Genomic Data Sharing (GDS) Policy to ensure the broad and responsible sharing of genomic

research data. NIH has longstanding policies to make data publicly available in a timely manner from the research activities that it funds. Once study database is locked, analysis of genomic/transcriptomic data may commence. RNA sequencing, and data deposition into dbGaP (adults only).

NIH's policy for data-sharing for federally funded genome-wide association studies requires that genotypic and phenotypic information from such studies will be made available through the NIH data repository designated as database of Genotypes and Phenotypes (dbGAP). Only coded de-identified data will be submitted to dbGAP. The data include the results of the transcriptomic data and selected demographic and clinical variables. dbGaP is divided into an open access area and a controlled access area. The open access area contains summary data only. Individual-level data and complete genomic summary data are kept in the controlled access area. Investigators who want access to data kept under controlled access (e.g., individual-level data) must submit a Project Request through dbGaP. Project Requests are reviewed by an NIH Data Access Committee, which focuses on whether the proposed research use of the requested data is consistent with data use limitations provided by the Institution that submitted the data to dbGaP.

10.13 COLLABORATIVE AGREEMENTS

10.13.1 Agreement Type

For the purpose of this trial, we have an executed clinical trial agreement (CTA), CTA#56584687, with Pfizer Inc.

A Memorandum of Understanding has been executed with the Clinical Research Center Department of Biostatics for biostatistical support for this study.

10.14 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIDCR has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

The NIH guidelines on conflict of interest will be distributed to all investigators.

The NIH and Dr. John O'Shea have a patent related to JAK inhibitors and receive royalties. The NIH and Dr. O'Shea have had a collaborative agreement and development award (CRADA) with Pfizer that pertains to JAK inhibition and tofacitinib. The NIH and Dr. O'Shea have an ongoing CRADA for new JAK inhibitors. We will submit appropriate information to the Deputy Ethics Committee (DEC) of the Clinical Center to determine conflict of interest in Dr. O'Shea's participation in this study.

No other investigators on the study team have any financial conflicts of interest to report.

The Principal Investigator will seek prospective and continuing NIH IRB review and approval for research collaborations in which coded samples (for which the investigators maintain the

key) are sent to non-NIH investigator(s). The PI will identify the names of the collaborating researchers and their affiliated institutions.

11 ABBREVIATIONS

AE	Adverse Event
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DHHS	Department of Health and Human Services
DMARDS	Disease modifying anti rheumatic drugs
DSMC	Data Safety Monitoring Committee
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator’s Brochure
ICH	International Council on Harmonisation
IDE	Investigational Device Exemption
IND	Investigational New Drug Application

IRB	Institutional Review Board
ITT	Intention-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIDCR	National Institute of Dental and Craniofacial Research
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

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13 ATTACHMENTS

Attachment A: Ocular Surface Disease Index© (OSDI)

Attachment B: Participant Weekly Medication chart

Attachment C: COVID-19 Safety and NIH Clinical Trial Information Card