

UPSTREAM SjD: A Global Phase 3 Study to Evaluate the Efficacy and Safety of Telitacicept in Patients With Primary Sjögren Disease



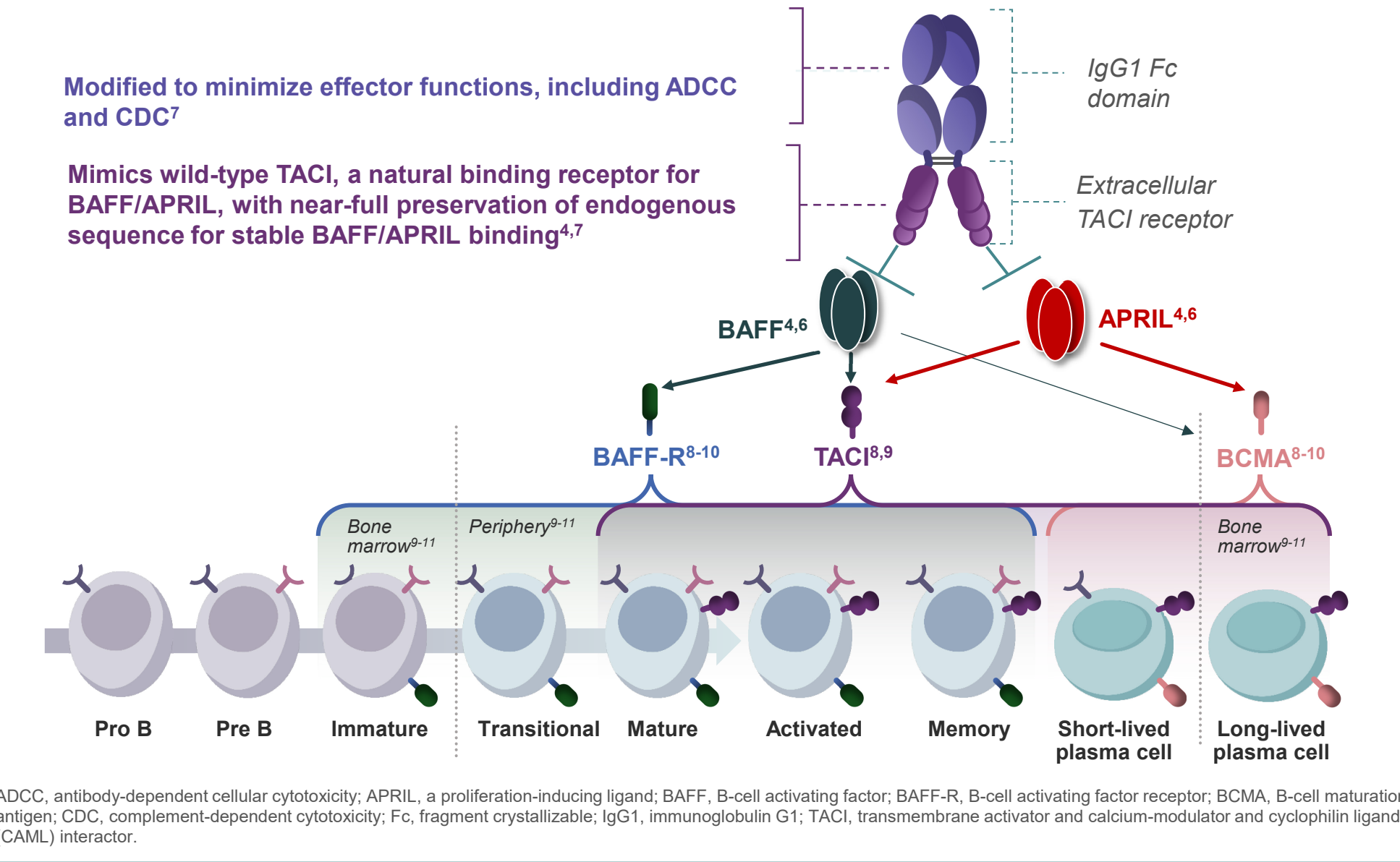
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BACKGROUND

- Sjögren disease (SjD) is a systemic autoimmune disease characterized by lymphocytic infiltration, B-cell hyperactivity, and immune-mediated exocrine gland dysfunction¹⁻⁴
- Lymphocytic infiltration of salivary and lacrimal glands predominantly causes xerostomia and keratoconjunctivitis sicca¹⁻⁵
- The symptom burden experienced by most patients includes pain, fatigue, and dryness, while approximately 30% of patients develop additional systemic manifestations¹⁻⁵
- Pathogenic B-cell and plasma cell activation drives tissue damage in SjD by promoting autoantibody production, immune complex formation, and antibody-independent mechanisms such as T-cell activation and cytokine production, ultimately leading to disease progression, systemic complications, and increased risk of lymphoma¹⁻³
- Current therapies for SjD are largely symptomatic or or rely on non-selective immunosuppression without targeting key drivers of disease pathogenesis highlighting the need for effective disease-modifying therapies^{1,4}
- Telitacicept is a TACI-Fc fusion protein that inhibits B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL)^{4,6,7}
- Through dual inhibition of BAFF and APRIL, telitacicept modulates upstream B-cell development and survival, and plasma cell function, reducing pathogenic autoantibodies implicated in SjD (**Figure 1**)^{4,6,7}

Figure 1. Telitacicept Is a Fusion Protein Based on the Human TACI Receptor Designed to Target BAFF and APRIL



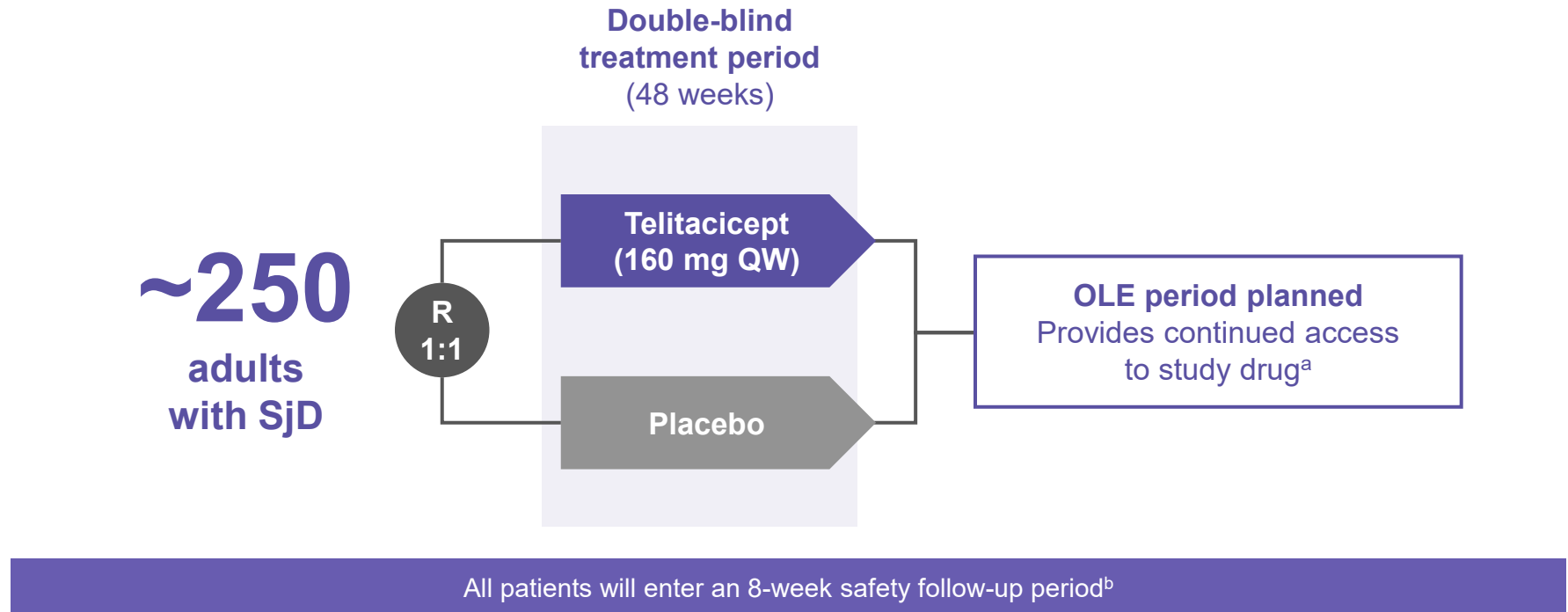
- Data from phase 2 (NCT04078386) and phase 3 (NCT05673993) studies of telitacicept conducted in China and sponsored by RemeGen Co., Ltd., demonstrated sustained efficacy and a generally well-tolerated safety profile in adults with primary SjD,¹²⁻¹⁵ which led to the approval of telitacicept in China
- The primary endpoint of change from baseline in EULAR Sjögren's syndrome disease activity index (ESSDAI) score at week 24 was met with statistical significance¹⁶
 - The change in ESSDAI score from baseline at week 24 was -4.4 in the telitacicept 160-mg group (least squares mean [LSM] difference of -3.8 ; $P<0.0001$), -3.0 in the telitacicept 80-mg group (LSM difference of -2.4 ; $P<0.0001$), and -0.6 in the placebo group¹⁶
 - Telitacicept was associated with greater reductions in EULAR Sjögren's syndrome patient reported index (ESSPRI) change from baseline scores at week 24 compared with placebo (160 mg: -1.94 ; 80 mg: -1.29 ; placebo: -0.42)¹⁶
 - In Stage B of the trial where patients could switch from placebo to telitacicept from weeks 24-48, similar responses to the first 24 weeks in ESSDAI and ESSPRI scores were observed at week 48¹⁶
 - Telitacicept was associated with predictable reductions in serum IgG, IgA, and IgM, and CD19+ B-cell counts compared with placebo¹⁵
- Here, the study design of an international, multicenter, randomized, double-blind, placebo-controlled phase 3 trial of telitacicept in adult participants with SjD is presented (NCT07404865)¹⁷

METHODS

Study Design

- UPSTREAM SjD will randomize ~250 patients with SjD 1:1 to receive either placebo or telitacicept subcutaneously weekly (**Figure 2**)
- UPSTREAM SjD will consist of a screening period of ≤ 4 weeks and a 48-week, double-blind, placebo-controlled phase
 - This is followed by a planned open-label extension (OLE) for those completing the study (**Figure 2**)
- All participants who discontinue the study are followed for an 8-week safety follow-up period

Figure 2. Study Design



^aFor patients who complete the double-blind treatment period in its entirety and who meet the eligibility criteria for enrollment in the OLE period. Participation in the OLE is voluntary, and informed consent specific to the extension study will be obtained prior to enrollment. ⁵Participants who complete the last dosing will have two follow-up visits at weeks 4 and 8 after the last dose of study medication to perform safety and immunogenicity assessments. OLE, open-label extension; QW, weekly; R, randomization; SjD, Sjögren disease.

Endpoints

- The primary endpoint is the change from baseline in ESSDAI at week 48
- Secondary efficacy endpoints include the following:
 - Proportion of participants whose ESSDAI score decreased from baseline by ≥ 3 at week 48
 - Proportion of participants whose ESSDAI score is < 5 at week 48
 - Change from baseline in ClinESSDAI score at week 48
 - Change from baseline in patient global assessment of disease activity (PtGA) and physician global assessment of disease activity (PhGA) at week 48
 - Change from baseline in the stimulated and unstimulated whole salivary flow at week 48
 - Change from baseline in ESSPRI score at week 48
 - Proportion of participants whose ESSPRI score decreased from baseline by ≥ 1 or 15% at week 48
 - Change from baseline in participant quality of life using the Short Form 36 (SF-36) at week 48
 - Change from baseline in Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) score at week 48
 - Proportion of participants who have a response on ≥ 3 domains in Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS) score at week 48
 - Proportion of participants who score ≥ 5 points in Sjögren's Tool for Assessing Response (STAR) at week 48
- Incidence of adverse events and evaluation of other vital signs and safety laboratory measurements will also be used to assess the safety and tolerability of telitacicept

Eligibility Criteria

- Inclusion and exclusion criteria are outlined in **Figure 3**
- Participants aged 18-75 years meeting 2016 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) criteria with an ESSDAI score ≥ 5 are eligible
- Anti-SSA/Ro positivity is required, though up to 10% may enroll with a positive salivary gland biopsy instead
- Stable background therapy is allowed: hydroxychloroquine for ≥ 8 weeks and low-dose prednisone (≤ 10 mg/day or equivalent) or one immunosuppressant for ≥ 4 weeks before screening
- Patients will be excluded if they have a chronic or acute infection

Figure 3. Inclusion and Exclusion Criteria

Key Inclusion Criteria	
Male or female	18+ Aged 18-75 years (both inclusive) at time of signing informed consent
Positive anti-SSA/Ro antibodies at screening ^a	ESSDAI score ≥ 5 at screening, excluding renal, pulmonary, and neurological domains
Prior exposure to biologics permitted with required washout	Participants on stable background therapy allowed stable low-dose oral corticosteroids, immunosuppressive agents, and NSAIDs
Exclusion Criteria	
Systemic autoimmune disease other than primary SjD that can better explain the majority of symptoms	Acute active infection requiring systemic therapies within 2 weeks of randomization or serious recent infection requiring intravenous antibiotics or hospitalization within 4 weeks of randomization
Significant, uncontrolled disease in any organ system not related to SjD (eg, cardiovascular disease, accelerated hypertension)	Current or history of primary immunodeficiency
History of malignancy within the last 5 years ^b	Prior intra-articular/intramuscular glucocorticoid or traditional/proprietary Chinese medicines within 4 weeks before randomization Prior intravenous glucocorticoid or cyclophosphamide or other alkylating agents within 8 weeks before randomization

^a10% of participants can qualify with negative anti-SSA/Ro with a biopsy (focus score ≥ 1). ^bExcept for adequately treated nonmelanoma skin cancers (basal or squamous cell) or carcinoma in situ of the cervix.
ACR, American College of Rheumatology; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; EULAR, European Alliance of Associations for Rheumatology; NSAID, nonsteroidal anti-inflammatory drug; SjD, Sjögren disease; SSA, Sjögren's syndrome type A.

Study Locations

- Study locations are shown in **Figure 4**

Figure 4. Study Locations



CONCLUSIONS

- An international, multicenter, randomized, double-blind, placebo-controlled phase 3 study is ongoing to evaluate the efficacy and safety of telitacicept in a global patient population
- Results from this study will expand on the phase 2 and 3 evidence generated in China by evaluating the efficacy of BAFF/APRIL inhibition with telitacicept in a global SjD population

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