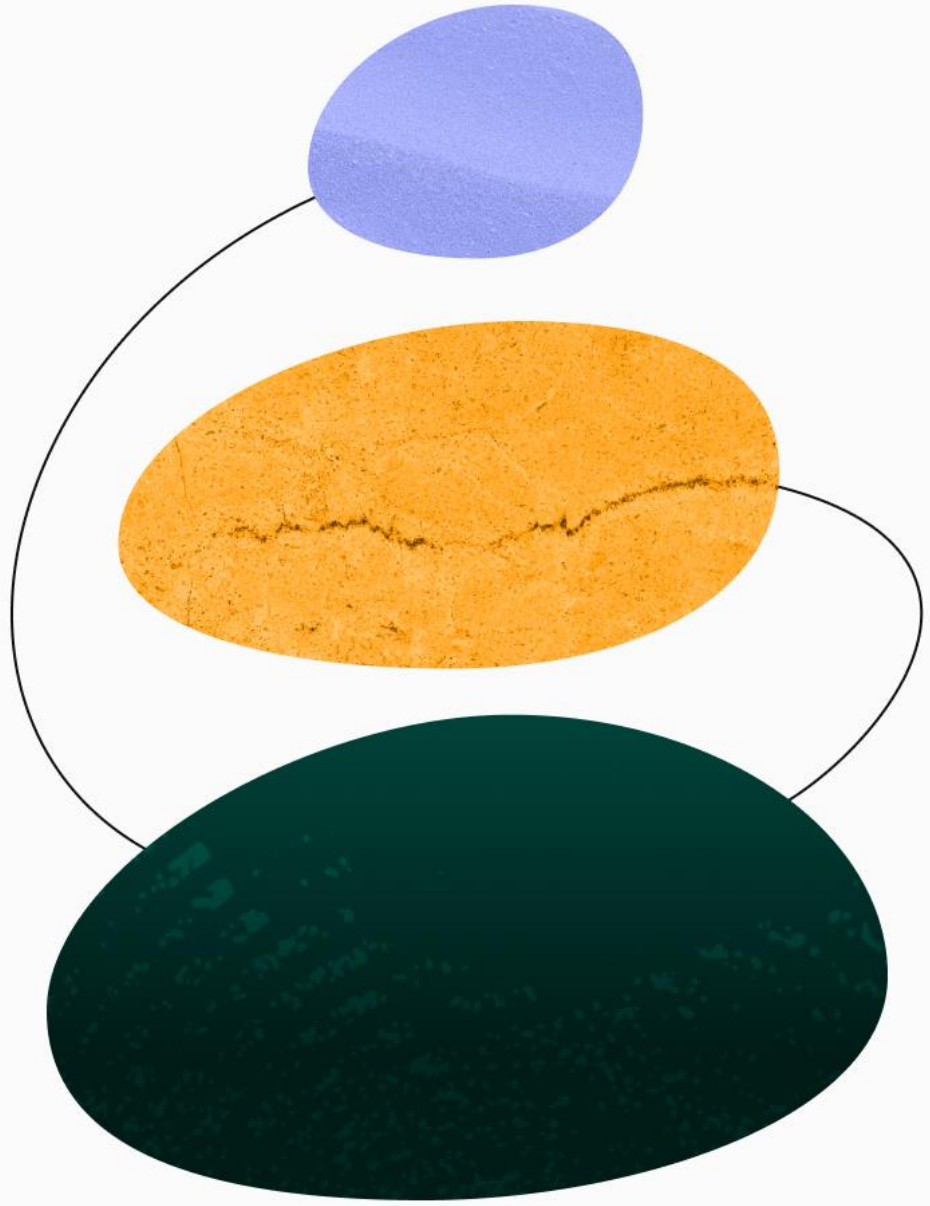
SPERO

July 2026

Corporate Presentation



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Developing Novel Medicines for Immune-Mediated Diseases

SP001, a third-generation Fc-silent anti-CD40L mAb with potential for development across a range of immune-mediated diseases

Lead indication in IgG4-related disease (IgG4-RD)

Established operational and public company infrastructure

Cash runway into 2H 2029

Key Investment Highlights: SP001

CD40L validated target	Target with human proof-of-concept in several autoimmune diseases
Phase 2 ready antibody	Completed 2 healthy volunteer trials and Phase 1b in Sjögren's disease
Potential best-in-class profile	Preclinical data show high potency compared to key competitors
Lead program in IgG4-RD	Differentiated mechanism compared to other B-cell targeting agents
Expansion opportunities	Sjögren's disease, additional rheumatological applications, and applications in non-rheumatological therapeutic areas

SP001 Development Plan for Rheumatological Disorders

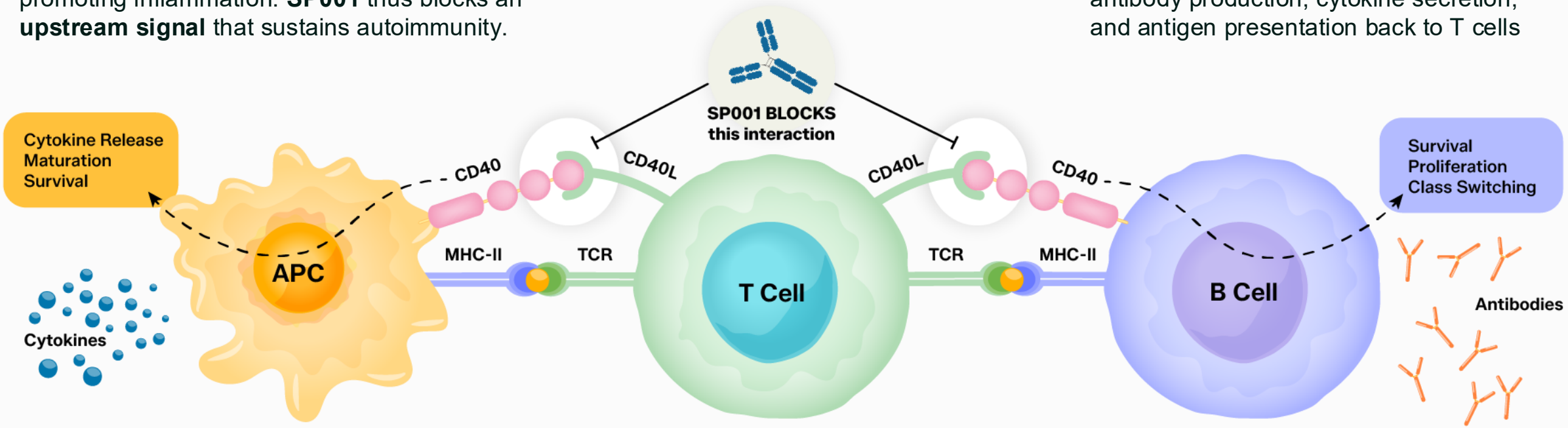
Indication	Exploratory	Phase 1	Phase 2	Phase 3	Catalyst / Expected timing
IgG4-RD					Phase 2 initiation Q2 2027
Sjögren's disease (Innovent)*					Phase 2 initiation by early 2027

* Development in greater China

CD40-CD40L System: A Master Regulator of Immunity

Antigen presentation: CD4 T cells present a CD40L "go" signal to antigen presenting cells (APC), promoting inflammation. **SP001** thus blocks an **upstream signal** that sustains autoimmunity.

B cells: SP001 blocks the **upstream CD40L signal** required for B cell survival, antibody production, cytokine secretion, and antigen presentation back to T cells



SP001 blocks the immune-activating CD40/CD40L signals between CD4 & CD8 T cells and between CD8 T cells and APC

Adapted from Laman JD, Molloy M, Noelle RJ. Switching off autoimmunity. Science. 2024 Aug 23;385(6711):827-829.
CD28/CD80–CD86 T-cell co-stimulation not shown for clarity

CD40L Mechanism Provides Multiple Development Opportunities

IgG4-Related Disease (IgG4-RD)

- Rare chronic disease with fibroinflammatory burden leading to organ failure
- Substantial treatment burden with high relapse rates
- Approved therapy and agents in development target B-cells
- **CD40L blockade affects both B and T cells; potential for use as chronic disease modifying therapy**

Potential Expansion Opportunities

- Phase 2 ready in Sjögren's disease
- Additional rheumatological diseases
- Exploratory applications in non-rheumatological therapeutic areas
- **Under-explored therapeutic areas may provide attractive entry points for longer-term expansion**

Sources: Wallace ZS et al. Ann Rheum Dis 2023; Stone JH et al. NEJM 2012; Lanzillotta M. et al. Rheumatology 2020.; De IgG4-RD DelveInsight Epidemiology, 2024.

Preliminary Indications Selected Offer Attractive Competitive Dynamics

SP001

Spero's Potential Development[1]	Ongoing Clinical Trials in Additional Indications[2]
IgG4-related disease	–
Sjögren's disease	Sjögren's disease
	Type 1 diabetes
	Systemic Lupus Erythematosus
	Transplant rejection
	Thyroid eye disease
	Multiple sclerosis

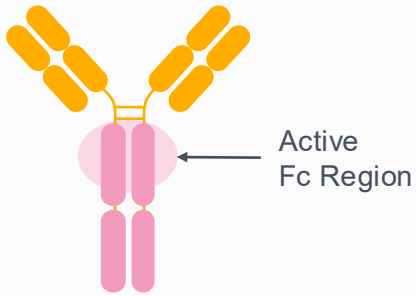
1,2. Lists may not be all inclusive. 2. Initiated by other industry sponsors developing CD40L targeting agents.

SP001 Overview

SPERO

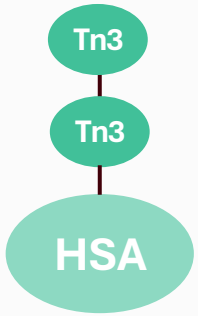
SP001 Is a Third-Generation, Fully Humanized, Fc-silent CD40L mAb

First-generation
(ex. Ruplizumab)



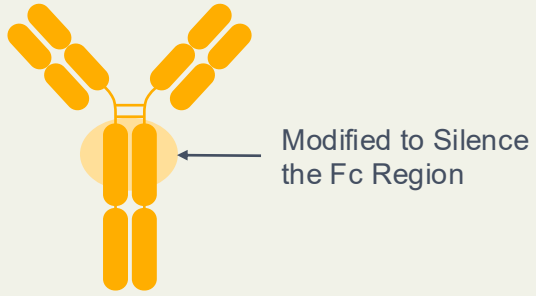
- Constant fragment (Fc) domain interacted w/ FcγRIIa on platelets, the putative MOA for the **increased risk of thrombosis**

Second-generation
(ex. Dazodalibep)



- Alternative modalities utilized non-antibody formats to avoid Fc receptor binding.
- Most assets lack beneficial drug properties of mAbs (half-life, low ADA, CMC, etc.)*

Third-generation
SP001



- SP001 is an IgG1 mAb designed to be **Fc-silent (ΔP-LALA)**
- No detectible Fc receptor and complement binding, eliminating platelet activation
- Normal FcRn interactions are preserved

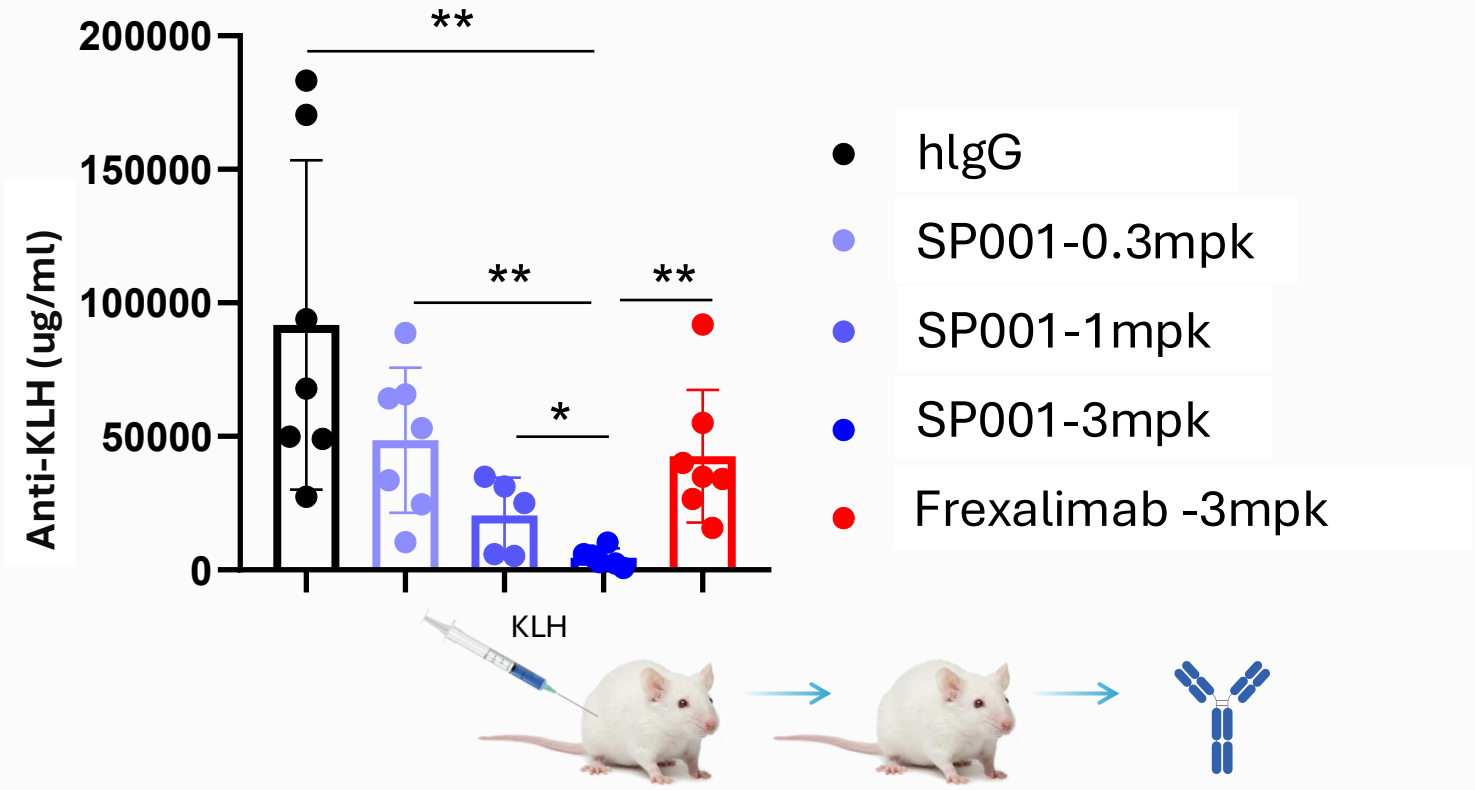
→ **IgG-like half-life**

SP001 combines high affinity and selectivity with preserved mAb functionality and PK properties, while engineering out the Fc-region pathogenic sequence

*Aglycosyl ruplizumab (Fc modified IgG1) considered 2nd Gen

SP001 Presents Potent Immune Suppression *In Vivo*

in-vivo immune response assay

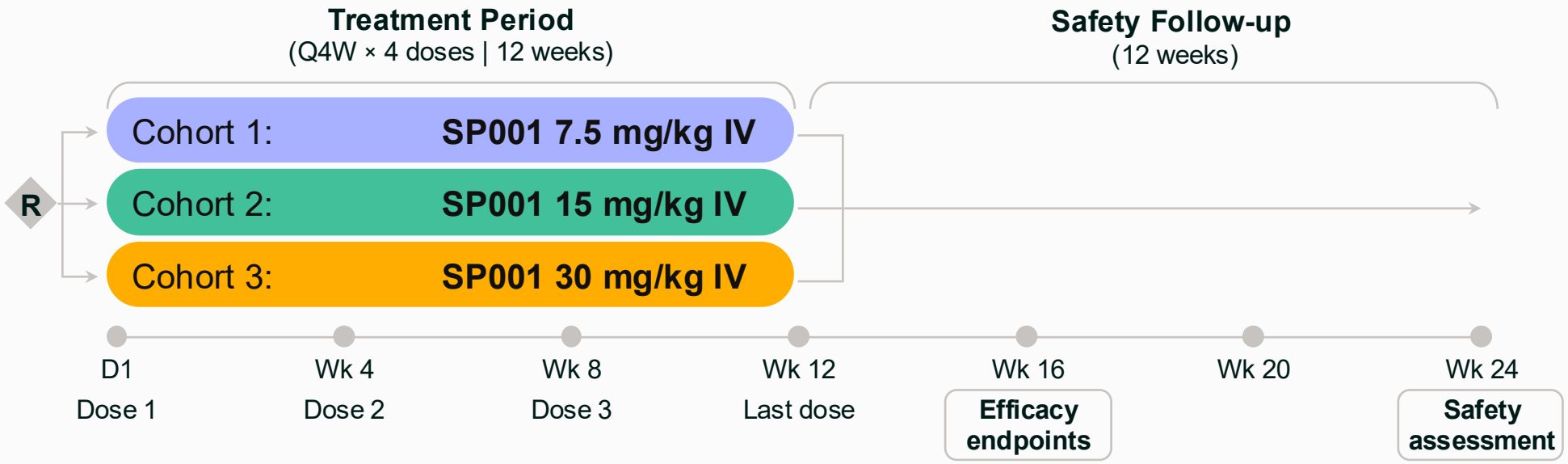


SP001 demonstrated superior immune suppression in anti-KLH immunization model compared to leading Phase 3 mAb

Anti-KLH (keyhole limpet hemocyanin) antibody evaluates immune function by measuring IgM (early response) and IgG (later response) antibodies following vaccination. Saghari M, Gal P, Ziagkos D, et al. A randomized controlled trial with a delayed-type hypersensitivity model using keyhole limpet haemocyanin to evaluate adaptive immune responses in man. Br J Clin Pharmacol. 2021;87:1953–1962.

Phase 1b[1] Characterized Safety/Tolerability, PK, and Efficacy Signals

Study Design: Double-blind*, placebo-controlled Multiple Ascending Dose (MAD) Study in Sjögren's disease



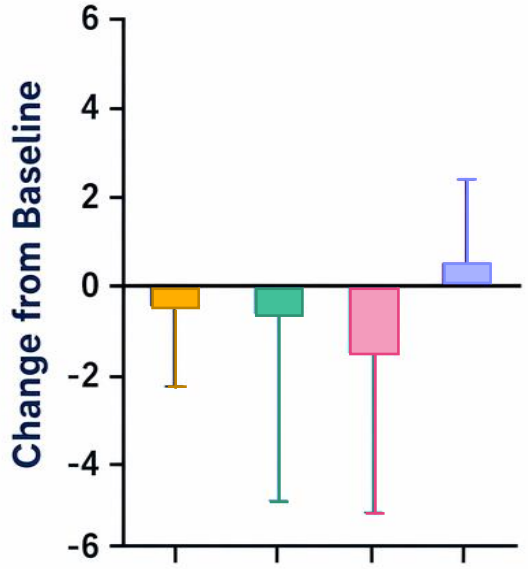
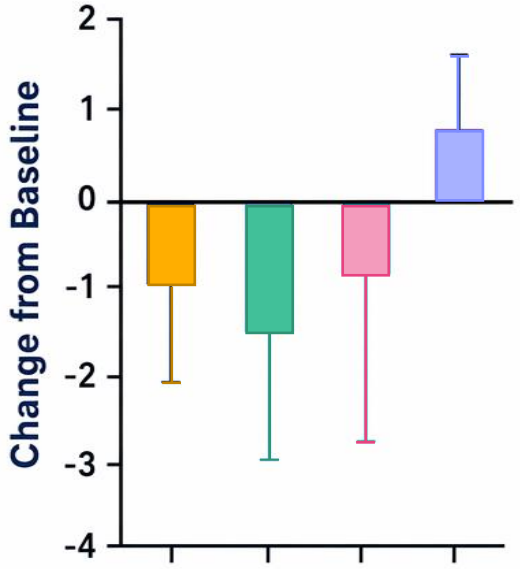
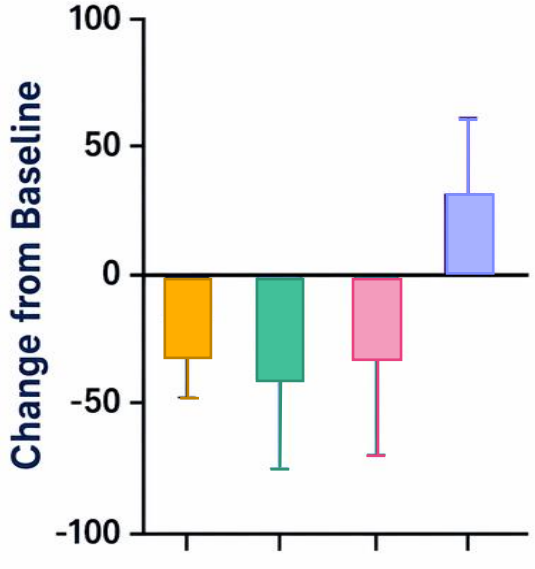
Primary Endpoint:	Safety and tolerability of 4 infusions of SP001 Q4W (screening to Week 24)
Secondary Endpoint:	PK characteristics and immunogenicity (screening to Week 24)
Other:	Efficacy (ESSDAI, ESSPRI)

1. Phase 1b MAD in Sjögren's disease patients completed in China. *Sponsor unblinded. N=10/cohort | Ratio 8:2 (active: placebo) within each cohort; two parallel placebo slots per cohort pooled as N=6. Poster presentation dated June 5, 2026, presented at the European Alliance of Associations for Rheumatology (the "2026 EULAR poster"), Method section; SP001 is known as IBI-355 prior to the closing of the in-licensing agreement with the licensor.

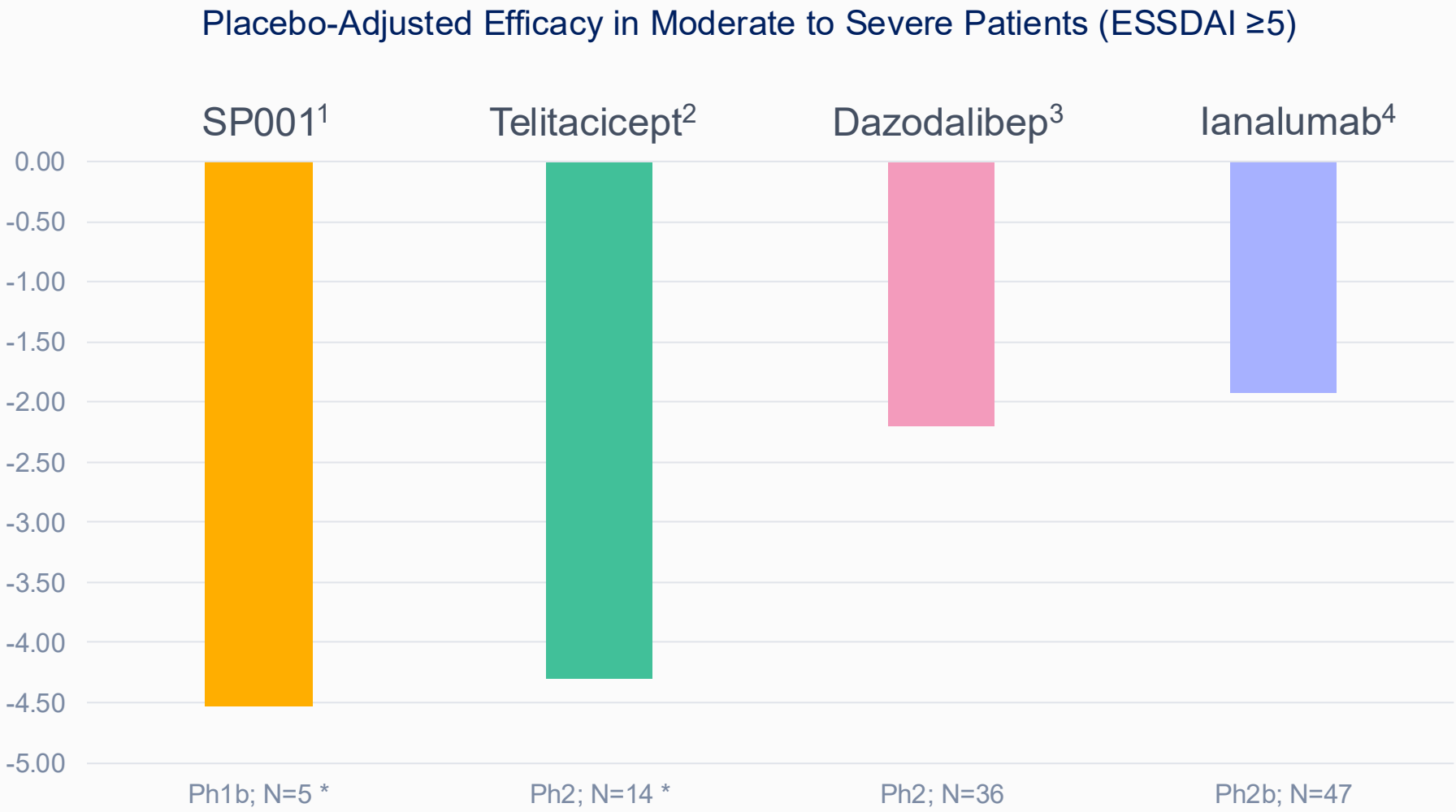
Safety Data Was Generally Benign

Safety Parameter	SP001 7.5 mg/kg (N=8)	SP001 15 mg/kg (N=8)	SP001 30 mg/kg (N=8)	SP001 Total (N=24)	Placebo (N=6)
Any Adverse Event (%)	75.0	87.5	75.0	79.2	100.0
Upper Respiratory Tract Infection (%)	50.0	50.0	50.0	50.0	33.3
Hyperlipidemia (%)	37.5	12.5	0.0	16.7	16.7
Serious Adverse Events	None reported				

Demonstrated Improvements in Disease Activity and B-cell Biomarkers

ESSDAI	ESSPRI	RF%	SP001
			7.5 mg/kg N=7 15 mg/kg N=8 30 mg/kg N=8 Placebo N=5
EULAR Sjögren's Syndrome Disease Activity Index	EULAR Sjögren's Syndrome Patient Reported Index	Rheumatoid factor, a classical autoantibody marker	

Ph1b Trial of SP001 Demonstrates Favorable Efficacy over Competitor Candidates



*Study performed in China 1. 2026 EULAR poster, Efficacy section. SP001 PBO group had 3 patients w/ ESSDAI ≥5; LS mean change from week 0 to week 24 = -0.67 2. Xu et al. Rheumatology (Oxford). 2024;63:698–705 3. St. Clair et al. Nat Med. 2024;30:1583–1592 4. Bowman et al. Lancet. 2022;399:161–171. The clinical data comparing SP001 and other products and product candidates are based on cross-study comparisons and are not based on any head-to-head clinical trials. Differences exist between trial designs, patient characteristics and other factors, and caution should be exercised in drawing any conclusions from a comparison of the data across studies as cross-study comparisons are inherently limited and such data may not be directly comparable.

Data to Date Support Continued Development

Safety

- SP001 well-tolerated across doses over the course of Phase 1b trial
- Preclinical toxicology and Phase 1 studies support continued development
- Chronic preclinical toxicology study currently underway to support longer duration dosing

Efficacy

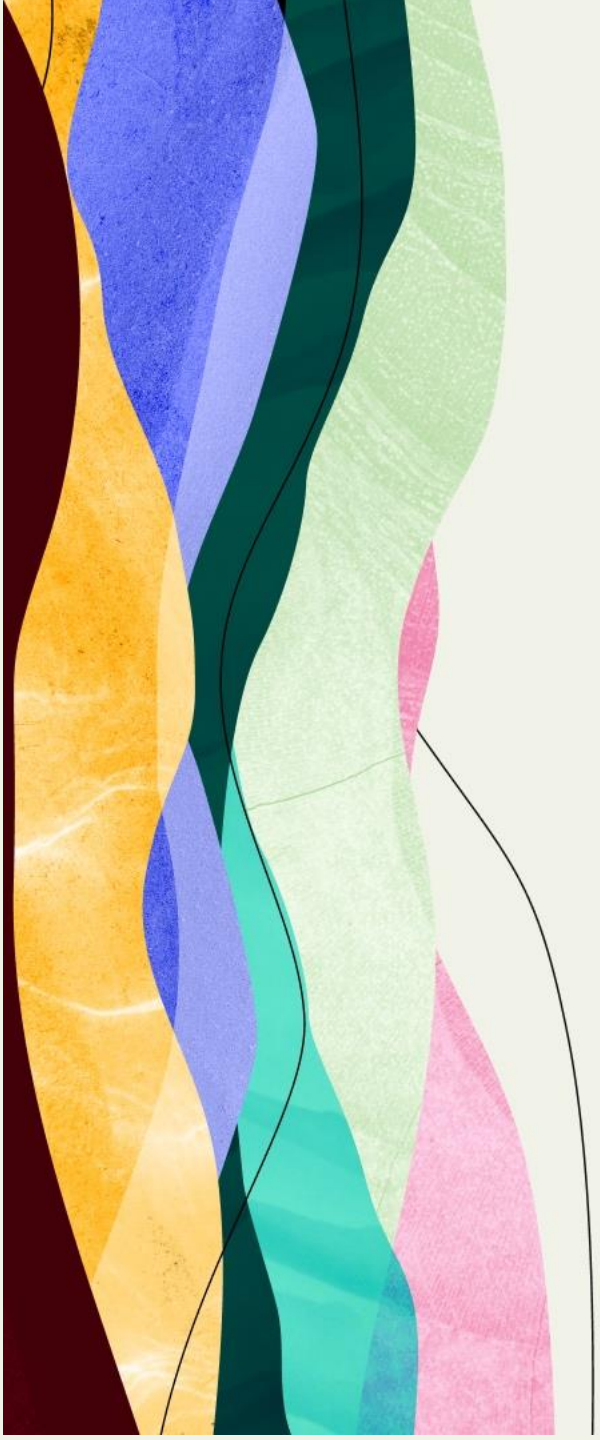
- Improvement in ESSDAI and ESSPRI scores vs placebo in all 3 doses
- Evidence of autoantibody reduction

Pharmacokinetics

- Linear PK across all doses
- Half-life of approximately 28 days
- 4-week (Q4W) dosing

Immunogenicity

- Low rate of anti-drug antibodies (ADA)

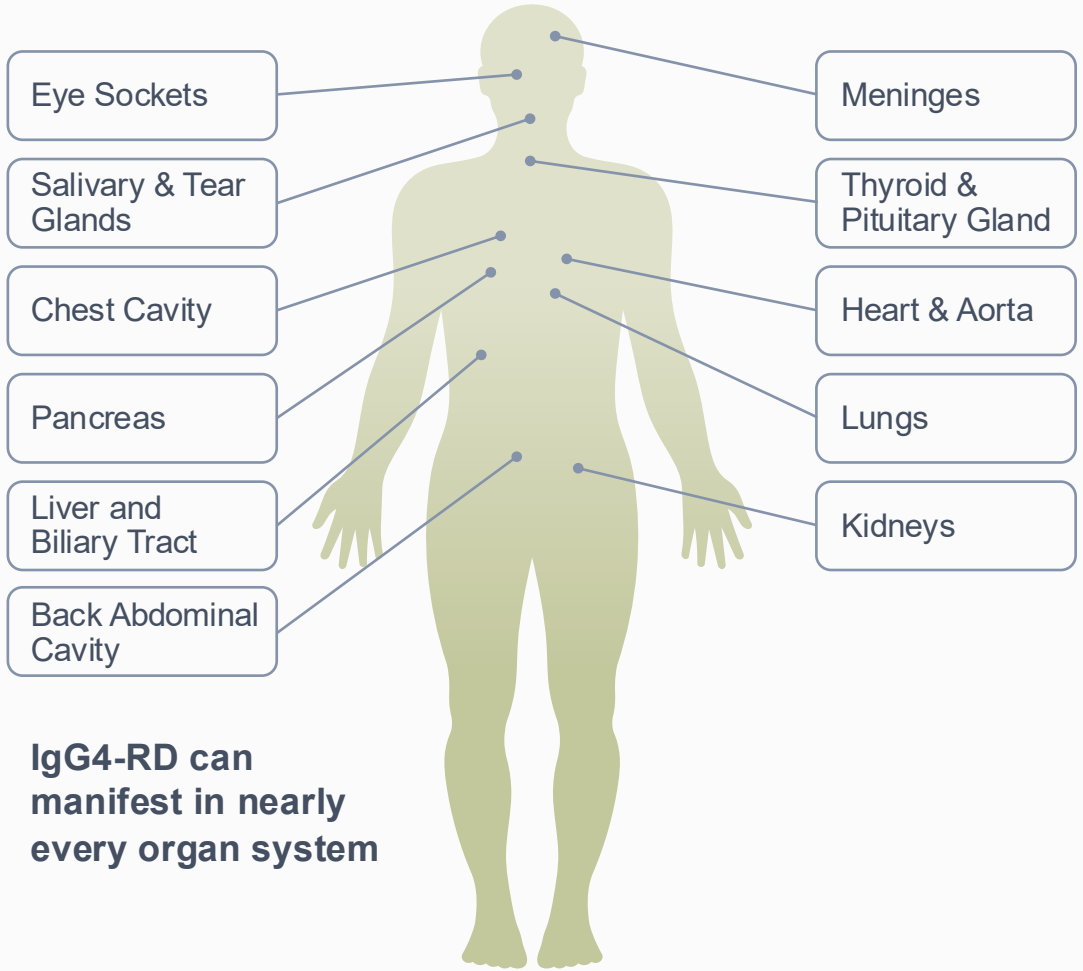


IgG4-Related Disease

IgG4-Related Disease: Chronic, Immune-Mediated Fibroinflammatory Condition

- Approximately 20K-40K diagnosed US patients
- Historically underdiagnosed with recently increasing diagnosis rates
- 60% patients present with organ damage at diagnosis
- Age of onset 50-70 years

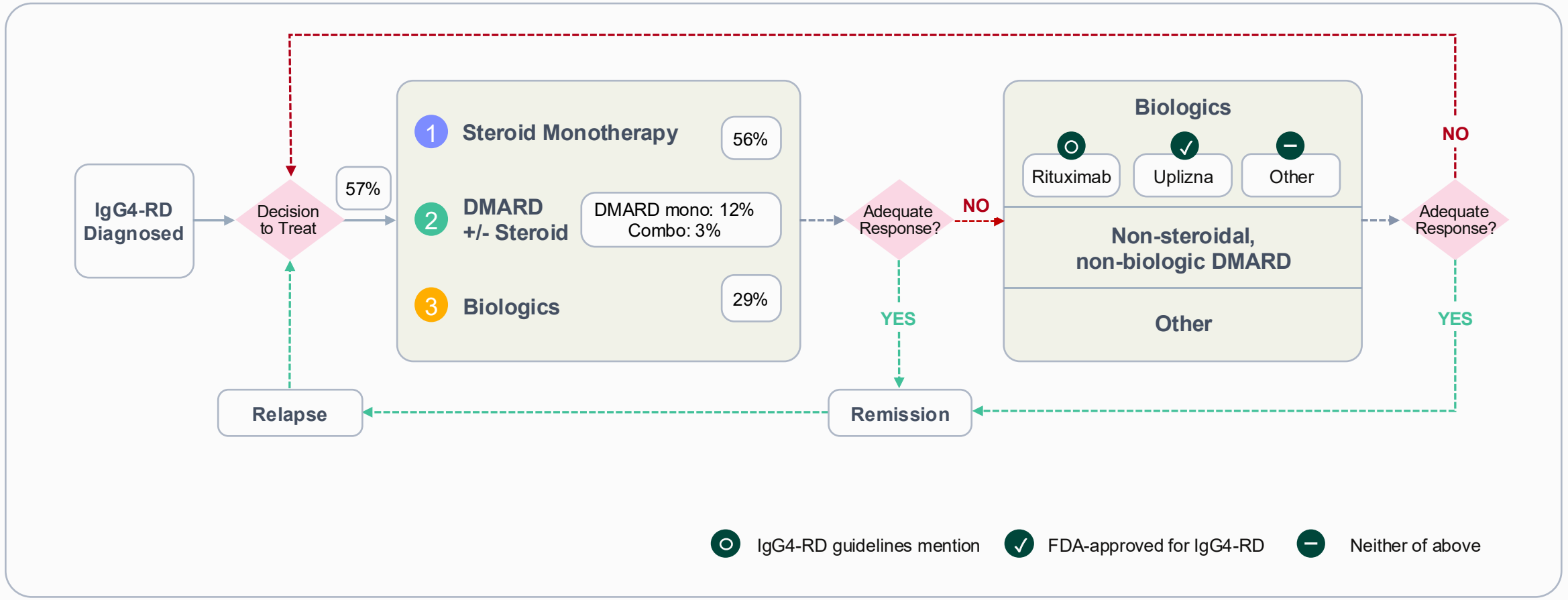
Progression to fibrosis and organ failure with under-treatment



IgG4-RD can manifest in nearly every organ system

Source: UpToDate; DelveInsight; Wallace ZS, et al. Ann Rheum Dis 2023;82:957–962

Current IgG4-RD Treatment Paradigm Results in Cycles of Relapse[1-4]



Current therapies manage active flares, but do not provide durable long-term control

Source: Syneos Health analysis. 1. Peyronel et al, Nature 2025. IgG4-related disease and other fibro-inflammatory conditions | Nature Reviews Rheumatology 2. Khosroshahi et al, A&R 20215 International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease - Khosroshahi - 2015 - Arthritis & Rheumatology - Wiley Online Library 3. Wallace et al, A&R 2019, bltfeda178976f1ad2a.pdf 4. Rare Disease Advisor: IgG4-RD updated Apr 2025 IgG4-Related Disease Treatment - Rare Disease Advisor. Abbreviations: DMARD- disease-modifying antirheumatic drugs. Note: Percentages represent share of patients receiving each therapy as 1L treated (n = 293).

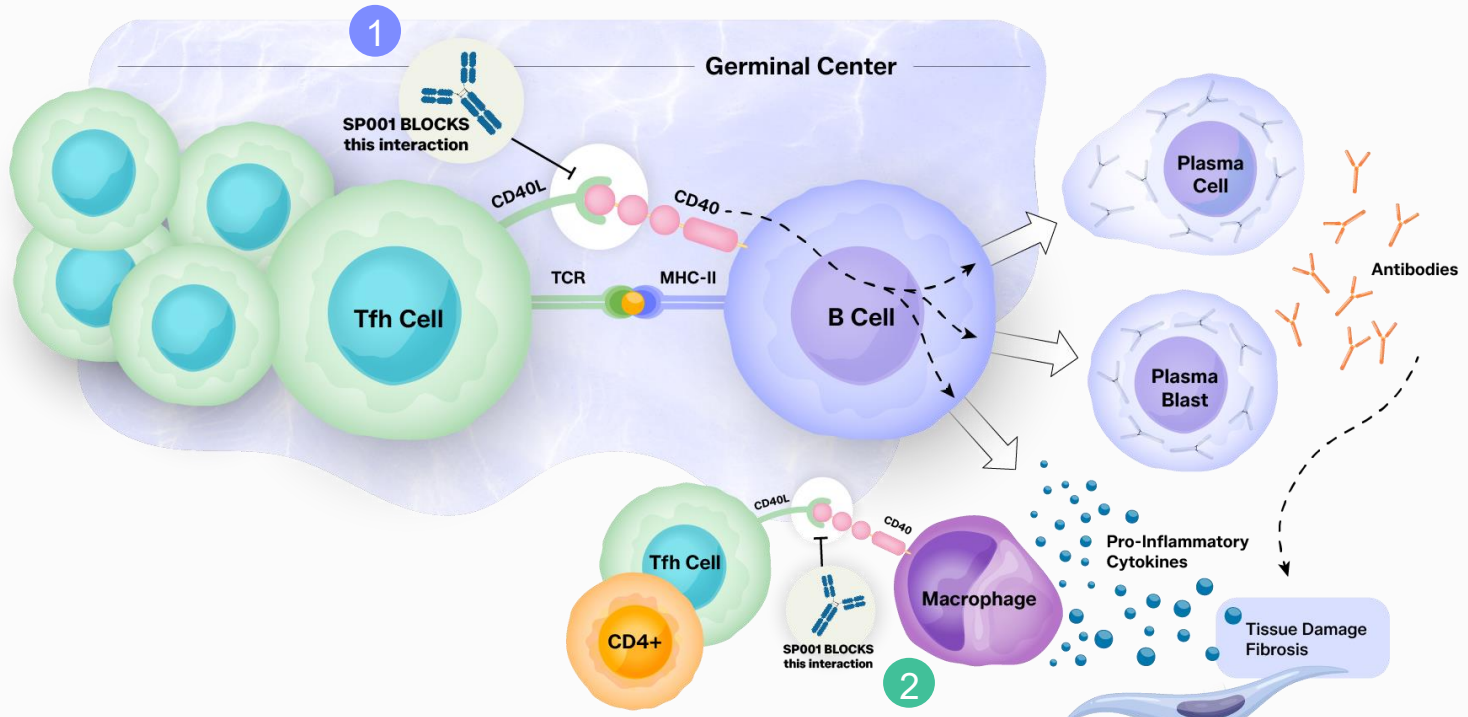
IgG4-RD Development Landscape Leaves Room for Differentiated Mechanism

Asset Name	Company	Target	Mechanism of Action	Route of Administration	Development Status
SP001	SPERO	CD40L	T–B cell co-stimulation	Intravenous	Phase 2 planned
Uplizna	AMGEN	CD19	B-cell depletion	Intravenous	Launched
Obexelimab	Zenas BioPharma	CD19+FcgRIIb	B-cell inhibition	Subcutaneous	Phase 3
Rilzabrutinib	sanofi	BTK	B-cell inhibition	Oral	Phase 3

Sources: Citeline and BioMedTracker

Biological Rationale for CD40L Inhibition in IgG4-RD

IgG4+ plasma cells accumulate in tissues and are associated with a chronic inflammation, but multiple cells contribute to pathologic fibrotic remodeling



1 SP001 designed to block CD40L driven **accumulation of IgG4 B cells / plasmablasts**

2 SP001 designed to block CD40L driven **antigen presentation and cytokines from APC**

CD40L sustains disease

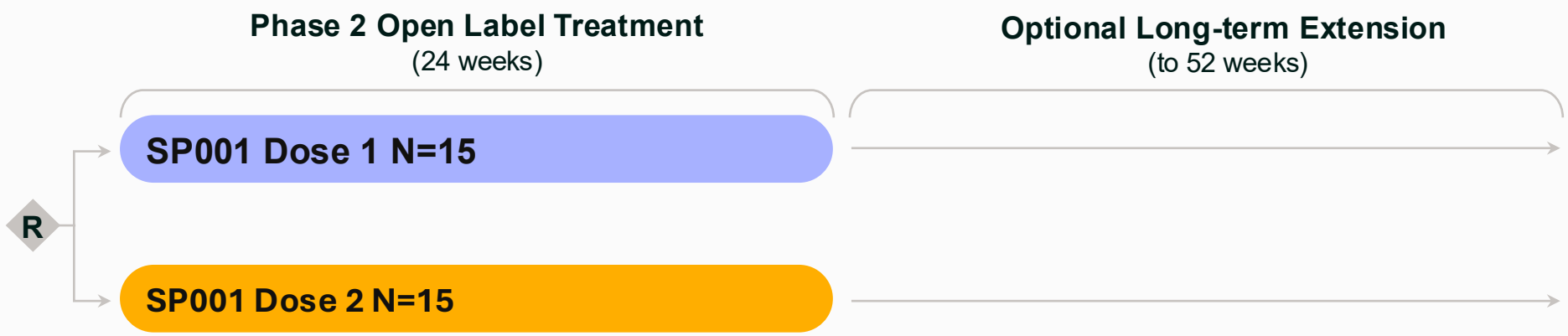
- Promotes local T cell : B cell interactions required for B cell accumulation and IgG4 class-switching
- Activates macrophages (APC) and B cells that are both potential sources of pro-fibrotic factors (e.g. TNF, IL-6, PDGF, chemokines, etc.)

Supporting evidence

- T cells in IgG4-RD express CD40L[1] and CD40 and CD40L are both elevated in IgG4-associated disease[2]
- CD40L is crucial for class switching of IgG4-RD patient cells in vitro[3]

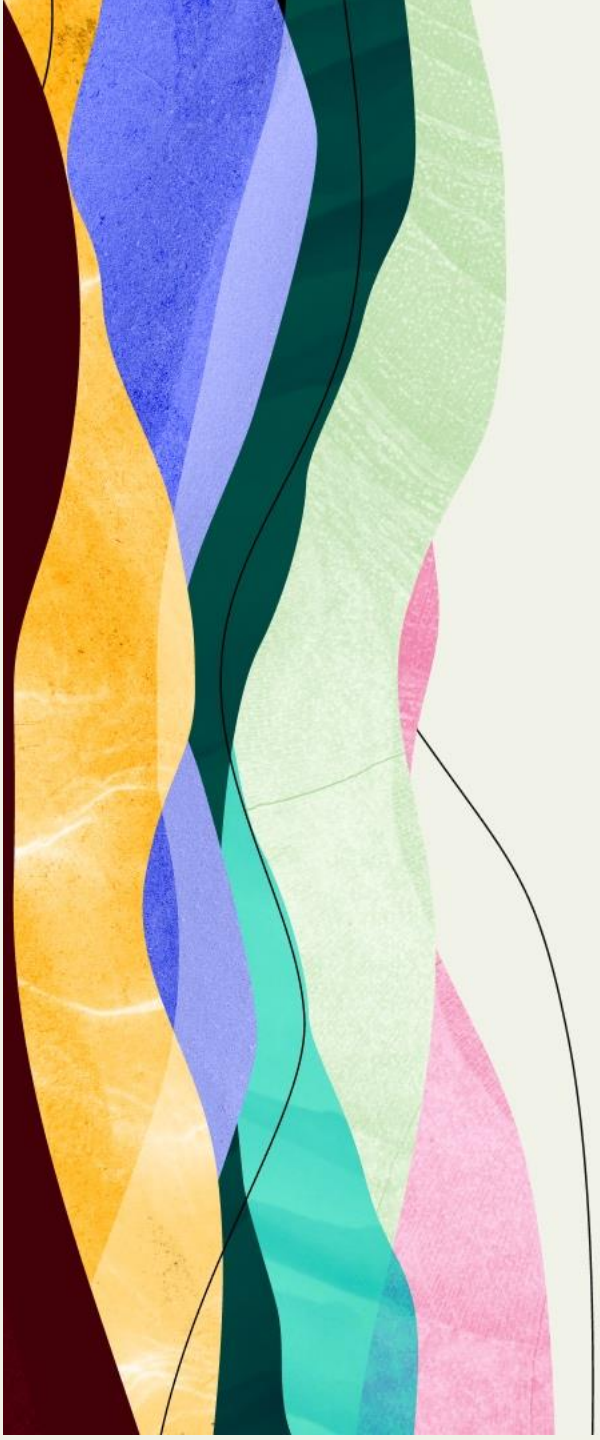
1. Borges T, Silva S. IgG4-related disease: How to place it in the spectrum of immune-mediated and rheumatologic disorders? Mod Rheumatol. 2020 Jul;30(4):609-616.; 2. Kudo-Tanaka E, et al., A case of Mikulicz's disease with Th2-biased cytokine profile: possible feature discriminable from Sjögren's syndrome. Mod Rheumatol. 2009;19(6):691-5. ; 3. Akiyama M, et al.. Enhanced IgG4 production by follicular helper 2 T cells and the involvement of follicular helper 1 T cells in the pathogenesis of IgG4-related disease. Arthritis Res Ther. 2016 Jul 13;18:167.

Phase 2 Study Designed to Establish Proof of Concept



Population:	IgG4-RD patients with >1 organ involved over time and active in at least one organ at enrollment Patients requiring steroids* protocol to incorporate a 4-week or 8-week steroid taper
Primary Endpoint:	Efficacy: Change from baseline in IgG4-RI at Week 24
Secondary Endpoint	Number of patients with TEAEs following dosing with SP001

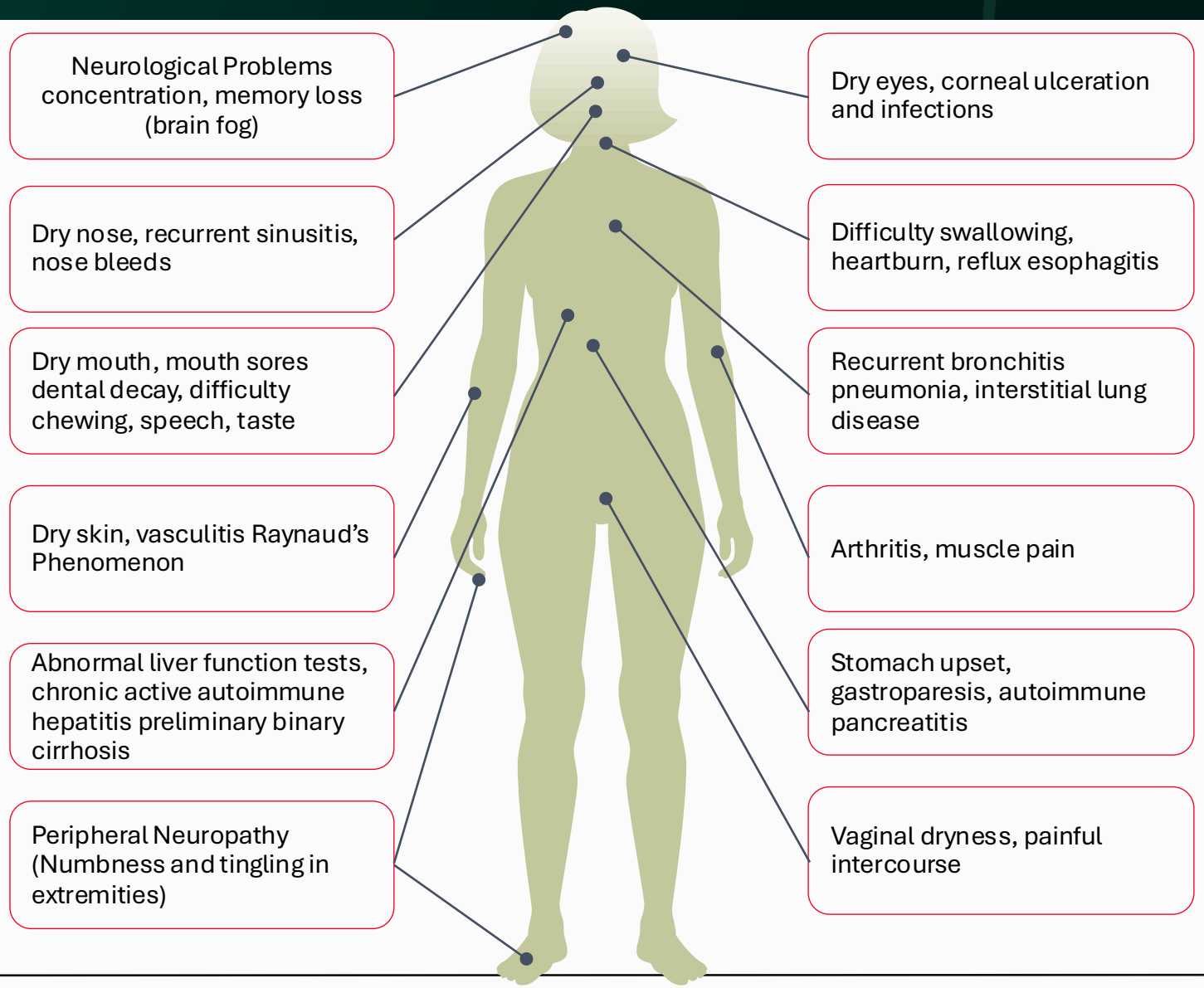
* Patient is flaring despite steroids



Expansion Opportunities

Sjögren's Disease Is a Complex Disorder with Limited Treatments Available

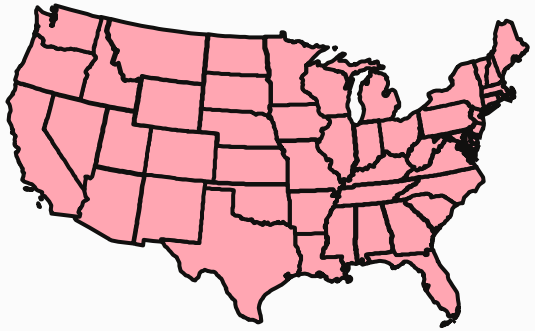
- Chronic autoimmune disease targeting **salivary and lacrimal glands**
- Patients with severe disease (e.g., systemic involvement) progress to **life-threatening complications including lymphoma, pulmonary diseases, neuropathy**
- Initially treated with **short term steroids**
- **Immunosuppressive therapies** (methotrexate, azathioprine, MMF, leflunomide) are used second line based on physician preference
- **Rituximab** failed a pivotal trial but is still widely used third line



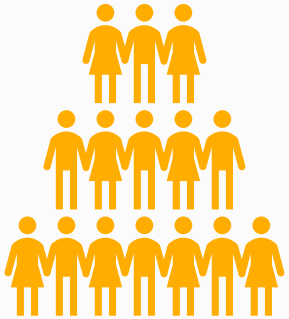
Sjögren's Disease: US Epidemiology and Unmet Needs

Epidemiology [1-4]

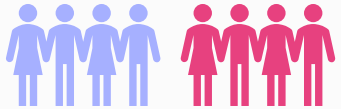
Up to 4M in the US[1] → **250K-400K** → **~50K-80K** addressable patients in US



2nd most common rheumatic autoimmune disease



diagnosed US patients[2,3,4]



Estimated addressable segment for novel therapies / biologics [5]

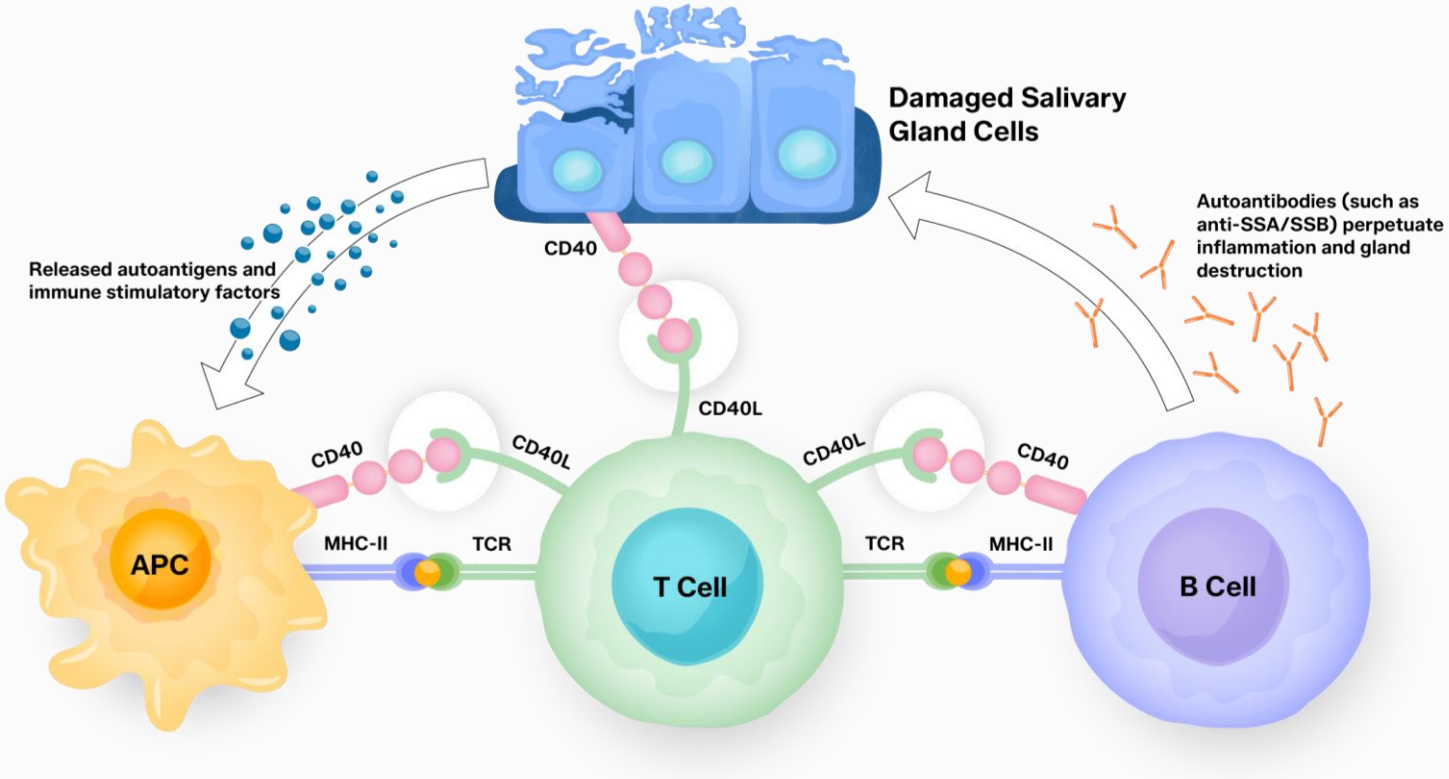
Unmet Needs

- Approved therapy for Sjögren's Disease
- Disease-modifying therapies with high safety bar enabling chronic treatment
- Treatment for both systemic disease and patient reported symptoms
- Clear patient stratification

Potential to capture additional patients as market evolves with new and improved therapies. Sources: 1.Sjögren's Foundation website – fast facts accessed 8 June 2026 (affecting as many as 4m Americans); 2. Willey C, Ali S, Alten R. Prevalence of Physician-Diagnosed versus Clinically Confirmed Primary Sjögren's syndrome (SS) Among Adults in the United States [abstract]. Arthritis Rheumatol. 2024; 76 (suppl 9); 3. Datamonitor Healthcare forecast tool accessed February 2026; 4. Helmick et al. Arthritis Rheum. 2008;58:15–25. 5. Brito-Zerón et al. Nat Rev Dis Primers. 2016;2:16047.

The Biological Rationale for CD40L in Sjögren's Disease Is Well Established

- Pathology is orchestrated by CD40L-expressing T cells
- **CD40L sustains disease** by
  - Stimulating immune activity from both antigen presenting cells and gland cells[1]
  - Promoting local production of destructive autoantibodies from B cells
- Supporting evidence indicates
  - CD40L expression is elevated in Sjögren's[2-4]
  - Inhibition of CD40L blocks local, autoreactive lymphoid structures, and reduces pathology in animal models of Sjögren's[5-6]
  - Importantly, CD40L inhibition has been clinically validated in published Ph2 studies[7]



1. Dimitriou et al. Clin Exp Immunol. 2002;127:386–392 2. Nakamura et al. Lab Invest. 1999;79:261–269 3. Goules et al. J Autoimmun. 2006;26:165–171 4. Belkhir et al. Scand J Immunol. 2014;79:37–42. 5. Wieczorek et al. Ann Rheum Dis. 2019;78:974–978 6. Voynova et al. ImmunoHorizons. 2018;2:54–66. 7. St. Clair et al. Nat Med. 2024;30:1583–1592.

Key Investment Highlights: SP001

CD40L validated target	Target with human proof-of-concept in several autoimmune diseases
Phase 2 ready antibody	Completed 2 healthy volunteer trials and Phase 1b in Sjögren's disease
Potential best-in-class profile	Preclinical data show high potency compared to key competitors
Lead program in IgG4-RD	Differentiated mechanism compared to other B-cell targeting agents
Expansion opportunities	Sjögren’s disease + applications in cardiology and endocrine disorders

Thank You

Spero Therapeutics
www.sperotx.com