Efficacy, Safety, Pharmacokinetics of Anti-CD40 Antibody Abiprubart in Patients with Rheumatoid Arthritis: a Phase 2, Randomized, Placebo-Controlled 12-week-treatment Proof-of-Concept Study

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Disclosure

I have the following relevant financial relationship to disclose:

- Shareholder and employee of Kiniksa Pharmaceuticals

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Learning Topics

By the end of this presentation, audience members will be able to:

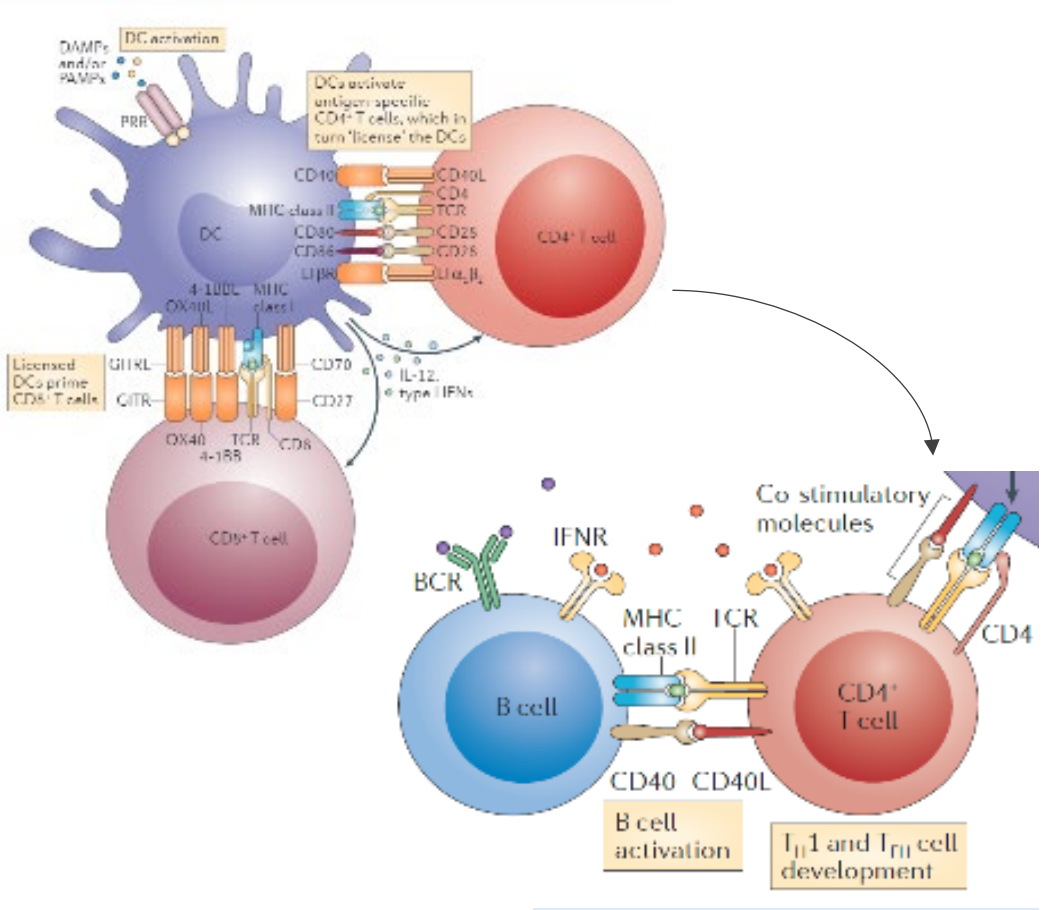
- Understand the mechanism of action for abiprubart
- Describe the study design and enrolled population of the phase 2 trial of abiprubart in rheumatoid arthritis
- Understand the clinical efficacy of abiprubart in rheumatoid arthritis
- Understand the safety profile of abiprubart
- Describe the ongoing phase 2b study in Sjögren's Disease

Mechanism of Action and Phase 1 Evidence

CD40/CD154 Interaction: Essential Immune Pathway for T-Cell Priming and T-Cell Dependent B-Cell Responses

- **CD40/CD154 interaction is implicated in a range of autoimmune diseases**

- **Abiprubart (KPL-404):**
  - Humanized monoclonal IgG4 antibody
  - Stabilized/functionally-silent Fc region
  - Binds to CD40 and inhibits the CD40/CD154 costimulatory interaction without lymphocyte depletion



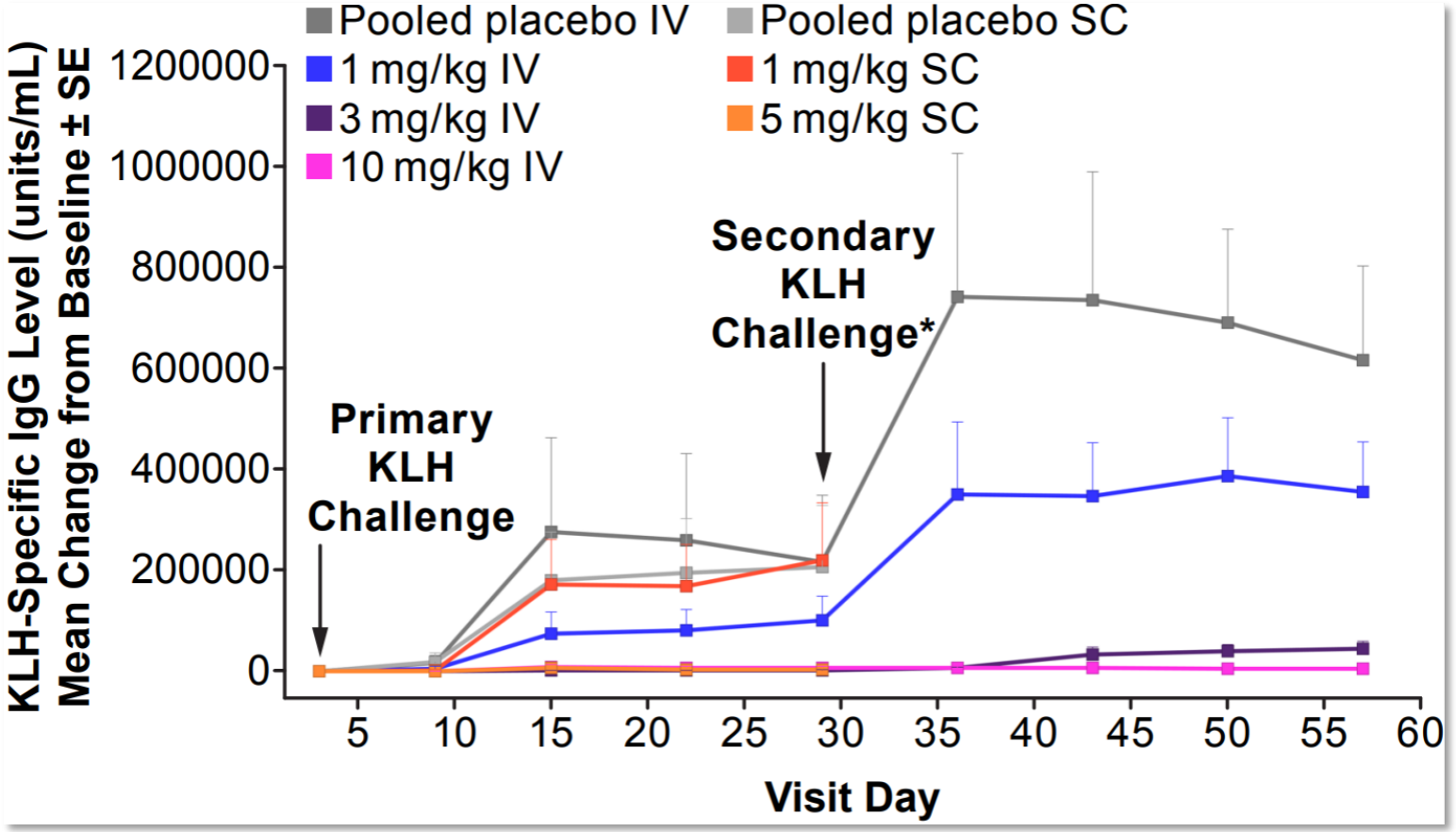
There are limited treatment options for patients with RA who have had an inadequate response to or are intolerant of currently-available biologics or targeted synthetic DMARDs.

Figures adapted with permission from: Summers deLuca, L., Gommerman, J. Fine-tuning of dendritic cell biology by the TNF superfamily. *Nat Rev Immunol* 12, 339–351 (2012). https://doi.org/10.1038/nri3193. and Desmet, C., Ishii, K. Nucleic acid sensing at the interface between innate and adaptive immunity in vaccination. *Nat Rev Immunol* 12, 479–491 (2012). https://doi.org/10.1038/nri3247.

DMARDs, disease-modifying anti-rheumatic drugs; RA, rheumatoid arthritis.

Abiprubart Demonstrated Prolonged TDAR Suppression in Phase 1

- **Phase 1 SAD study in healthy participants[1]**
  - Abiprubart was well tolerated
  - Dose-dependent duration of full CD40 target engagement
  - Sustained dose-dependent TDAR suppression with both SC and IV administration
- **High-concentration liquid formulation supports chronic SC administration**



Single abiprubart 5 mg/kg SC dose suppressed TDAR for at least 30 days[1]

*Only intravenous cohorts were rechallenged with KLH on Day 29.

KLH, keyhole limpet hemocyanin; RA, rheumatoid arthritis; SAD, single ascending dose; SC, subcutaneous; TDAR, T-cell dependent antibody response; IV, intravenous.

Figure used with permission from: *J Pharmacol Exp Ther*. First-in-Human Phase 1 Randomized Trial with the Anti-CD40 Monoclonal Antibody KPL-404: Safety, Tolerability, Receptor Occupancy, and Suppression of T-Cell-Dependent Antibody Response. *J Pharmacol Exp Ther*. 2023;387(3):306-314. https://doi.org/10.1124/jpet.123.001771

1) Samant M, Ziemniak J, Paolini JF. First-in-Human Phase 1 Randomized Trial with the Anti-CD40 Monoclonal Antibody KPL-404: Safety, Tolerability, Receptor Occupancy, and Suppression of T-Cell-Dependent Antibody Response. *J Pharmacol Exp Ther*. 2023;387(3):306-314.

Abiprubart Phase 2 Rheumatoid Arthritis Study Design

Global Phase 2 Trial of Abiprubart in Rheumatoid Arthritis

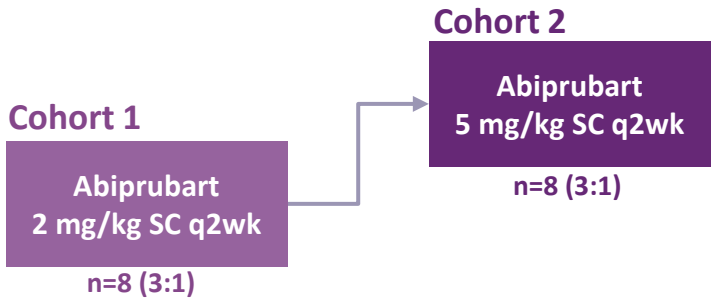
PATIENT POPULATION:

- Active RA; bDMARD AND/OR JAKi therapy for ≥ 3 months with inadequate response or discontinued due to intolerance or toxicity

DISEASE CRITERIA:

- ≥ 6 swollen joints and ≥ 6 tender joints at screening and baseline visits; hsCRP ≥ 3 mg/L; seropositivity for RF and/or ACPA

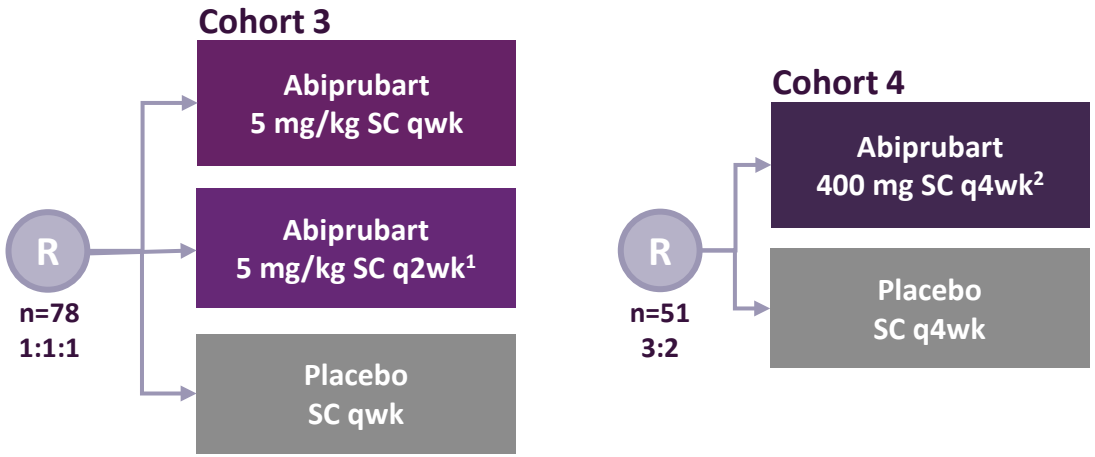
PHARMACOKINETICS (PK) LEAD-IN



PK Lead-In: Cohorts 1-2

- Placebo recipients from Cohorts 1 and 2 were pooled
- Primary Endpoints:
  - Incidence of treatment-emergent adverse events (TEAEs)
  - Pharmacokinetics (C_{max}, $AUC_{(0-t)}$)
- Secondary Efficacy Endpoint:
  - Change from baseline in DAS28-CRP at Week 12

PROOF-OF-CONCEPT



Proof of Concept: Cohorts 3-4

- Primary Efficacy Endpoint:
  - Change from baseline in DAS28-CRP at Week 12
- Secondary Endpoints :
  - Incidence of treatment-emergent adverse events (TEAEs)
  - Pharmacokinetics (C_{max}, $AUC_{(0-t)}$)
- Other Endpoints:
  - Change from baseline in RF
  - ACR20

Phase 2 Study Objectives:

- Evaluate the safety and PK of multiple doses of abiprubart SC in RA patients vs. placebo (Cohorts 1 & 2)
- Evaluate the efficacy of abiprubart SC vs. placebo in RA patients (Cohorts 3 & 4)

[1]The 5 mg/kg SC q2wk group received weekly administrations of alternating active investigational product and matching blinded placebo.
[2]The Cohort 4 abiprubart 400mg SC q4wk group includes a 600mg loading dose on Day 1.
ACPA, anti-citrullinated protein antibodies; ACR20, assessment measuring 20% improvement in the American College of Rheumatology response criteria for rheumatoid arthritis symptoms; AUC, area under the curve; bDMARDs, biological disease-modifying anti-rheumatic drugs; hsCRP: high sensitivity c-reactive protein; JAKi: Janus kinase inhibitor; PD, pharmacodynamics; PK, pharmacokinetics; qwk, every week; q2wk, every other week; q4wk, every four weeks; R, randomization; RF, Rheumatoid Factor; SC, subcutaneous.

Results of Abiprubart Phase 2 Rheumatoid Arthritis Trial

Select Baseline Demographics And Disease Characteristics

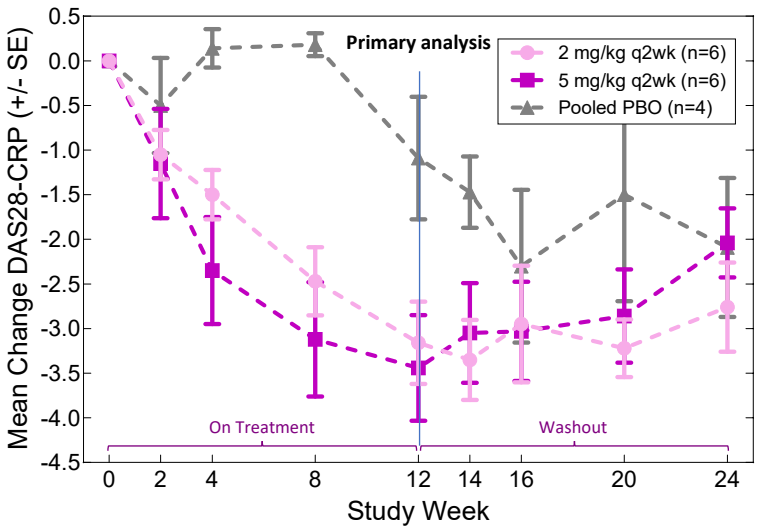
	Cohort 3[1]			Cohort 4[1]	
	Abiprubart 5 mg/kg SC qwk (n=27)	Abiprubart 5 mg/kg SC q2wk (n=25)	Placebo (n=26)	Abiprubart 400 mg SC q4wk (n=31)	Placebo (n=20)
Baseline Demographics					
Mean Age, years	58.5 (9.7)	60.0 (10.1)	57.6 (9.9)	58.8 (9.5)	58.3 (11.8)
Sex % (Male/Female)	18.5/81.5	20.0/80.0	7.7/92.3	19.4/80.6	25.0/75.0
Race					
White %; (n)	92.6 (n=25)	92.0 (n=23)	92.3 (n=24)	83.9 (n=26)	85.0 (n=17)
Black or African American %; (n)	3.7 (n=1)	8.0 (n=2)	7.7 (n=2)	9.7 (n=3)	5.0 (n=1)
Asian %; (n)	3.7 (n=1)	0	0	6.5 (n=2)	10.0 (n=2)
Region					
United States %; (n)	29.6 (n=8)	28.0 (n=7)	38.5 (n=10)	32.3 (n=10)	20.0 (n=4)
Europe %; (n)	62.9 (n=17)	52.0 (n=13)	50.0 (n=13)	58.1 (n=18)	55.0 (n=11)
South Africa %; (n)	7.4 (n=2)	20.0 (n=5)	11.5 (n=3)	9.7 (n=3)	25.0 (n=5)
Inadequate response to classes of prior advanced targeted therapy					
≤ 1 class	81.5 (n=22)	80.0 (n=20)	80.8 (n=21)	93.5 (n=29)	85.0 (n=17)
≥ 2 classes	18.5 (n=5)	20.0 (n=5)	19.2 (n=5)	6.5 (n=2)	15.0 (n=3)
Baseline Disease Characteristics					
Mean DAS28-CRP	5.58 (0.81)	5.92 (1.03)	5.98 (0.98)	5.65 (0.94)	5.89 (0.78)
Mean Duration of RA, years	12.24 (11.46)	13.50 (8.43)	15.47 (10.22)	11.70 (10.29)	10.77 (9.07)
Mean Rheumatoid factor, U/mL	165.21 (209.48)	183.45 (191.53)	154.62 (188.09)	117.43 (158.96)	210.57 (239.80)
Anti-Cyclic Citrullinated Peptide %; (n)					
Positive/Indeterminate	77.8 (n=21)	80.0 (n=20)	76.9 (n=20)	74.2 (n=23)	85.0 (n=17)
Negative	22.2 (n=6)	20.0 (n=5)	23.1 (n=6)	25.8 (n=8)	15.0 (n=3)

Data cutoff: 27-JUN-2024; data are presented as mean (standard deviation) or percentage (n = number of patients).
[1]Modified Intention to Treat (mITT) analysis population (all randomized subjects who received at least one dose of study drug and had a baseline assessment and at least one post-baseline assessment for the primary efficacy endpoint).
RA, rheumatoid arthritis; SD, standard deviation.

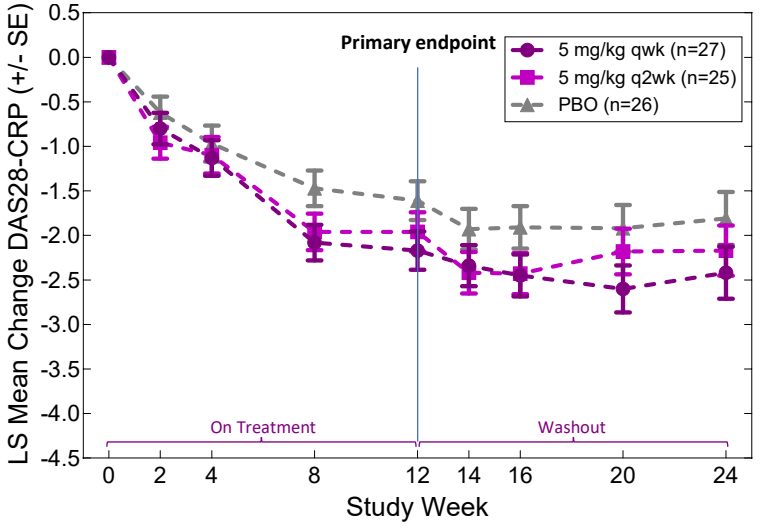
Phase 2 Trial of Abiprubart in RA Met Primary Efficacy Endpoint

Change from Baseline in DAS28-CRP vs Placebo at Week 12

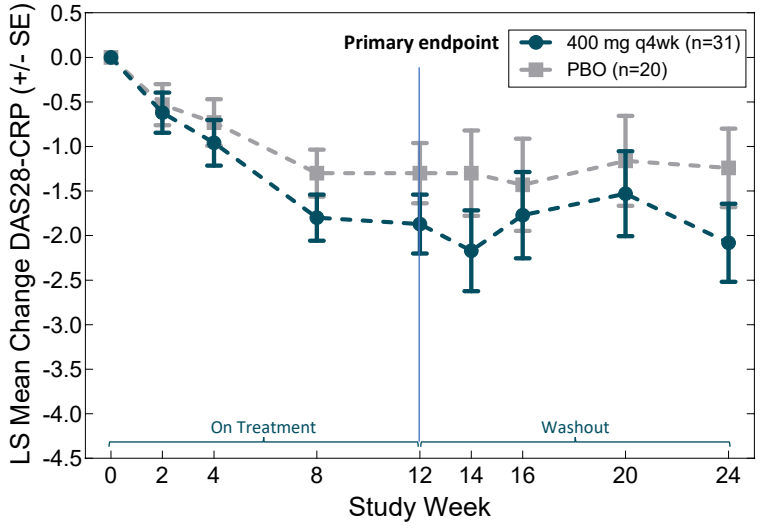
Cohort 1 & 2
DAS28-CRP Mean Change from Baseline[1*]



Cohort 3
DAS28-CRP LS Mean Change from Baseline[1,2*]



Cohort 4
DAS28-CRP LS Mean Change from Baseline[1,2*]



Primary Efficacy Results at Week 12

Cohort 1: 2 mg/kg SC q2wk
Mean Difference: -2.07, p=0.031
- Abiprubart (n=6): -3.16
- Pooled Placebo (n=4): -1.09

Cohort 2: 5 mg/kg SC q2wk
Mean Difference: -2.35, p=0.034
- Abiprubart (n=6): -3.44
- Pooled Placebo (n=4): -1.09

Cohort 3: 5 mg/kg SC qwk
LS Mean Difference: -0.57, p=0.047
- Abiprubart (n=27): -2.17 [-2.60, -1.74]
- Placebo (n=26): -1.61 [-2.04, -1.17]

Cohort 3: 5 mg/kg SC q2wk
LS Mean Difference: -0.36, p=0.212
- Abiprubart (n=25): -1.96 [-2.40, -1.52]
- Placebo (n=26): -1.61 [-2.04, -1.17]

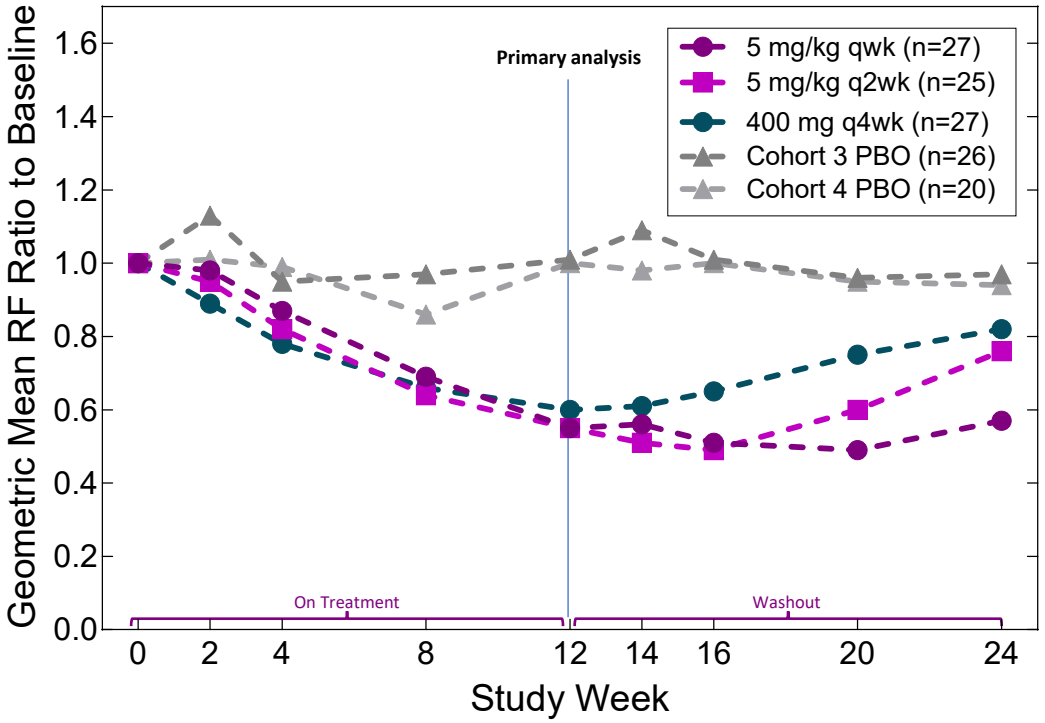
Cohort 4: 400 mg SC q4wk
LS Mean Difference: -0.58, p=0.109
- Abiprubart (n=31): -1.87 [-2.54, -1.21]
- Placebo (n=20): -1.30 [-1.98,-0.62]

[1]Final data.
[2]Modified Intention to Treat (mITT) analysis population (all randomized subjects who received at least one dose of study drug and had a baseline assessment and at least one post-baseline assessment for the primary efficacy endpoint).
CI, Confidence Interval; DAS28-CRP, Disease Activity Score of 28 Joints Using C-reactive Protein; LS, least squares; RA, rheumatoid arthritis; SC, subcutaneous.; PBO, placebo

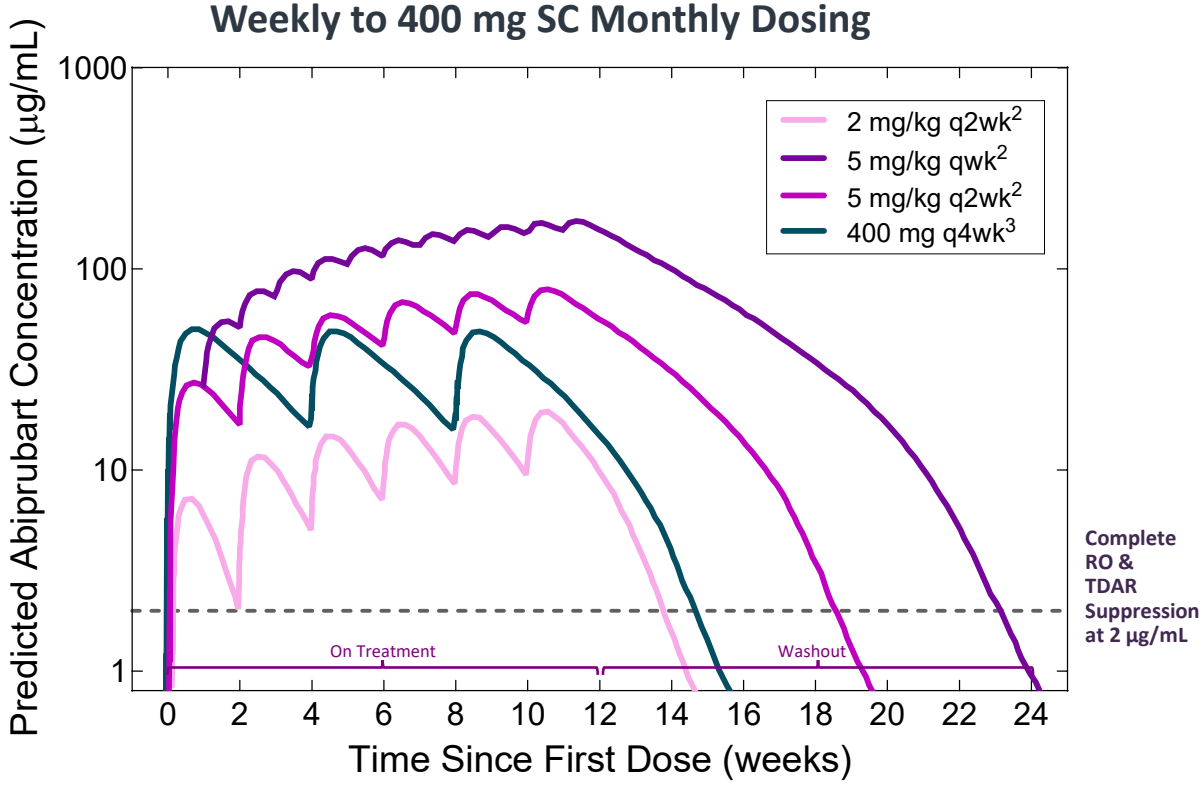
Pharmacodynamics & Pharmacokinetics: Statistically Significant Similar Magnitude Reductions in Rheumatoid Factor at all SC Dose Intervals

RF is primarily an IgM autoantibody which not only serves as a disease marker but also provides a mechanism-related PD marker of anti-CD40 target engagement

Abiprubart Reduced Rheumatoid Factor Geometric Mean Ratio to Baseline[1]

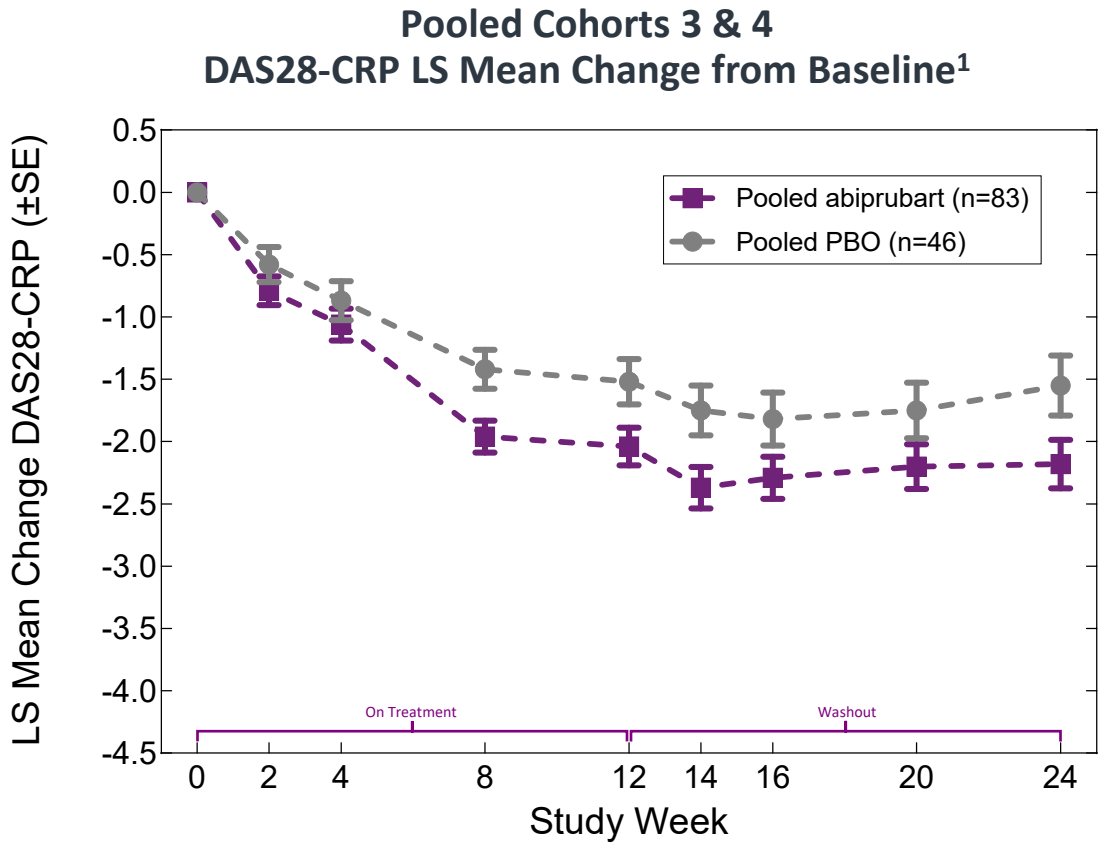


PK Modeling Data[4]: Full Target Engagement from 5 mg/kg SC Weekly to 400 mg SC Monthly Dosing



[1]In both Cohort 3 abiprubart dose groups (5 mg/kg SC weekly and 5 mg/kg SC biweekly) (p<0.0001); in the Cohort 4 abiprubart dose group (400 mg SC monthly) (p=0.0003).
[2]All doses were subcutaneous.
[3]The Cohort 4 abiprubart 400mg SC q4wk group includes a 600mg loading dose on Day 1.
[4]Generated based on PK data from Cohorts 1-4 of Ph2 RA trial & Ph1 data from healthy volunteers.
PK, pharmacokinetics; RA, rheumatoid arthritis; RO, receptor occupancy; SC, subcutaneous; TDAR, T-cell dependent antibody response; PBO: Placebo.

Pooled Analysis: Abiprubart Significantly Reduced DAS28-CRP Over Time



LS Mean Difference: -0.52, nominal p=0.010

- Pooled abiprubart (n=83): -2.04 [-2.34, -1.74]
- Pooled placebo (n=46): -1.52 [-1.88, -1.16]

[1]Modified Intention to Treat (mITT) post-hoc analysis population (all randomized subjects who received at least one dose of study drug and had a baseline assessment and at least one post-baseline assessment for the primary efficacy endpoint).
PBO, placebo

Abiprubart was Well-Tolerated - No Dose-related Adverse Experiences

Category[2]	Cohort 3[1]			Cohort 4[1]	
	Abiprubart 5 mg/kg SC qwk (n=27)	Abiprubart 5 mg/kg SC q2wk (n=25)	Placebo (n=26)	Abiprubart 400mg SC q4wk (n=31)	Placebo (n=20)
Treatment Emergent Adverse Events (TEAEs)[3]	44.4 (n=12)	24.0 (n=6)	30.8 (n=8)	29.0 (n=9)	40.0 (n=8)
Drug Related TEAE[4]	7.4 (n=2)	8.0 (n=2)	7.7 (n=2)	9.7 (n=3)	5.0 (n=1)
TEAEs by Maximum severity[5]	44.4 (n=12)	24.0 (n=6)	30.8 (n=8)	29.0 (n=9)	40.0 (n=8)
Mild	29.6 (n=8)	12.0 (n=3)	15.4 (n=4)	12.9 (n=4)	25.0 (n=5)
Moderate	14.8 (n=4)	12.0 (n=3)	15.4 (n=4)	16.1 (n=5)	15.0 (n=3)
Severe	0	0	0	0	0
Potentially Life Threatening	0	0	0	0	0
Fatal	0	0	0	0	0
Serious TEAEs (SAE)	3.7 (n=1)[6]	0	0	0	0
Drug-Related SAEs[3]	0	0	0	0	0
TEAEs Leading to Death	0	0	0	0	0
TEAEs Leading to Dose Interruption	3.7 (n=1)	0	3.8 (n=1)	0	0
TEAEs Leading to Treatment Discontinuation	0	0	0	3.2 (n=1)	5.0 (n=1)
TEAEs of Special Interest	3.7 (n=1)	4.0 (n=1)	0	3.2 (n=1)	10.0 (n=2)
Injection Site Reaction	3.7 (n=1)	4.0 (n=1)	0	6.5 (n=2)	0

[1]Safety Population: all randomized subjects who received at least one dose of study drug.
[2]All categories are represented in percentages.
[3]Defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug during treatment period.
[4]Definitely related or possibly related, as assessed by the investigator.
[5]Each subject has only been represented with the maximum severity.
[6]Transient monaural deafness at Week 12, not related, resolved with pulse-dose steroids.

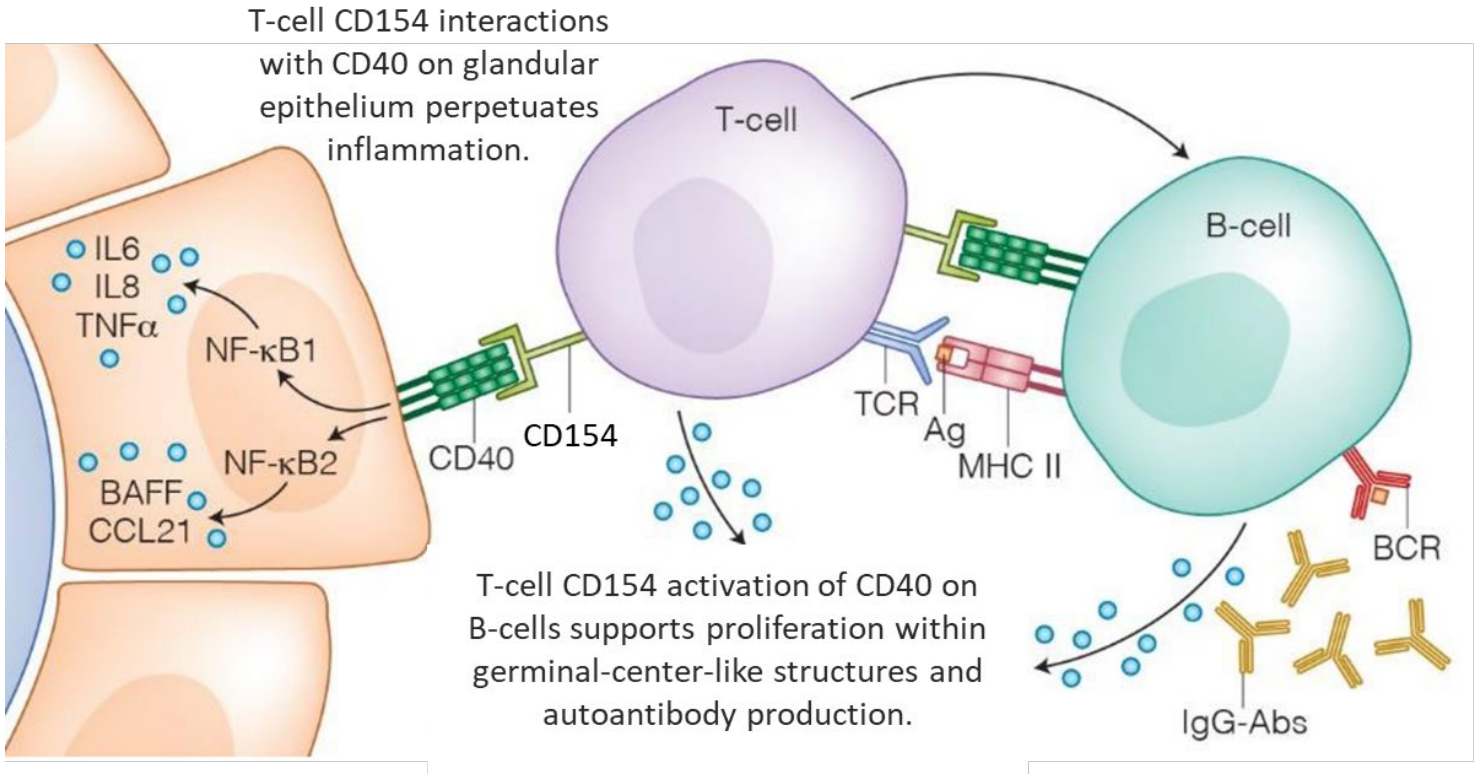
Ongoing Phase 2b Study in Sjögren's Disease

The CD40/CD154 axis may play a central role mediating SJD pathology

Abiprubart is likely to disrupt co-stimulation and the disease supporting role of salivary gland stromal cells

SJD pathogenesis involves multiple factors[1-3]

- Autoreactive B and T cells escape regulatory suppression
- Salivary epithelial cells express co-stimulatory molecules, including CD40, and can present autoantigen to T-cells
- T-cells support formation of germinal center-like structures and B cell activation, resulting in:
  - Affinity maturation
  - Clonal expansion
  - Differentiation of plasmablasts/plasma cells to produce autoantibodies
- Plasma cell niche maintained by salivary gland stromal cells



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Abs, antibodies; Ag, antigen; BAFF, B cell-activating factor; BCR, B-cell receptor; CCL21, C-C motif chemokine ligand 21; SJD, Sjögren's Disease; TCR, T-cell receptor.

1) Nocturne G, Mariette X. B cells in the pathogenesis of primary Sjögren syndrome. *Nat Rev Rheumatol*. 2018;14(3):133-145.

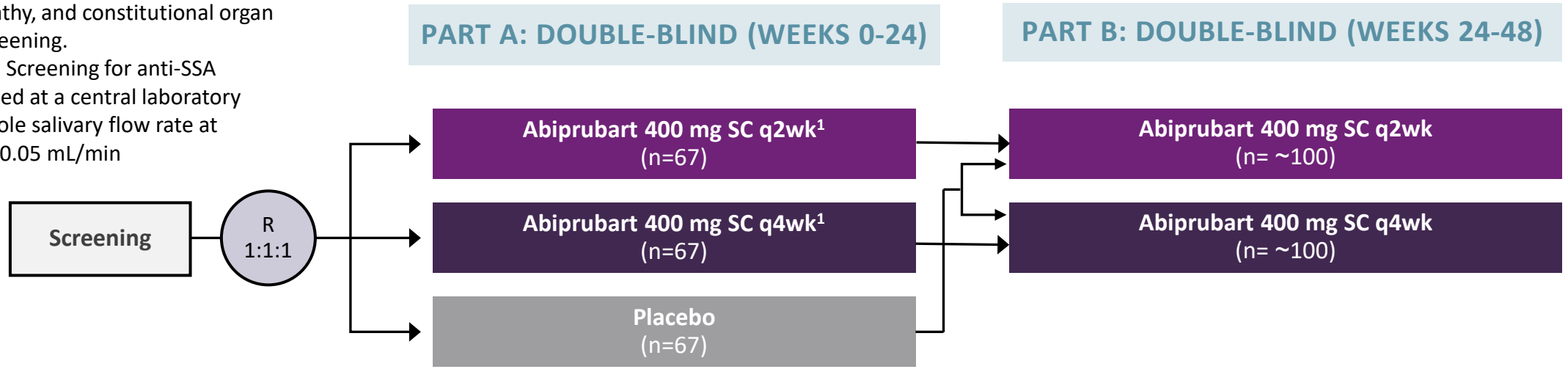
2) Dimitriou ID, et al. CD40 on salivary gland epithelial cells: high constitutive expression by cultured cells from Sjögren's syndrome patients indicating their intrinsic activation. *Clin Exp Immunol*. 2002;127(2):386-392.

3) Maslinska M, Kostyra-Grabczak K. The role of virus infections in Sjögren's syndrome. *Front Immunol*. 2022;13:823659. Published 2022 Sep 6.

Ongoing Phase 2 Trial of Abiprubart in Sjögren's Disease

PATIENT POPULATION

- Diagnosis of Sjögren's Disease according to 2016 ACR-EULAR Classification Criteria
- ESSDAI value ≥ 5, counting only the biological, hematological, articular, cutaneous, glandular, lymphadenopathy, and constitutional organ domains at screening.
- Seropositive at Screening for anti-SSA antibodies tested at a central laboratory
- Stimulated whole salivary flow rate at Screening of ≥ 0.05 mL/min



Endpoints

Primary: Change from baseline in EULAR Sjögren's Disease Activity Index (ESSDAI) at Week 24

Key secondary endpoint: Proportion of Sjögren's Tool for Assessing Response (STAR) responders (≥ 5 points) at Week 24

Other secondary endpoints: Change from baseline in ESSDAI over time, proportion of STAR responders (≥ 5 points) over time, and changes from baseline in stimulated salivary flow, unstimulated salivary flow, ESSPRI, Schirmer's test, clinESSDAI, FACIT-Fatigue, and EQ-5D 5L at Week 24 and over time

[1]Both abiprubart dosing groups include an 800mg loading dose on Day 1

ACR, American College or Rheumatology; clinESSDAI, clinical EULAR Sjögren's Syndrome Disease Activity Index; EQ-5D 5L, EuroQol 5-Dimension 5-level questionnaire; ESSPRI, EULAR Sjogren's Syndrome Patient Reported Index; EULAR European League Against Rheumatism; FACIT Fatigue Scale, Functional Assessment of Chronic Illness Therapy for measuring fatigue during daily activities over the past week; q2wk, every other week; q4wk, every four weeks; R, randomization; SC, subcutaneous; SSA, Sjögren's-syndrome-related antigen A autoantibodies.

Key Takeaways

- **Phase 2 RA study met its primary efficacy endpoint**
  - In refractory RA patients, abiprubart treatment resulted in a statistically significant reduction in DAS28-CRP at Week 12 vs. placebo in the 5mg/kg SC weekly dosing group
- **Comparable activity across weekly, biweekly, and monthly dosing**
  - Reduction in RF was statistically significant and similar in magnitude across dosing intervals
  - Nominally statistically significant reduction in DAS28-CRP in post-hoc analysis of pooled data
- **Sustained abiprubart treatment was well-tolerated**
- **Results support further clinical development of abiprubart in autoimmune diseases in which the CD40/CD154 costimulatory interaction has been implicated**
  - The phase 2b study in Sjögren's Disease is currently enrolling patients

DAS28-CRP, Disease Activity Score of 28 Joints Using C-reactive Protein; RA, rheumatoid arthritis; RF, rheumatoid factor; SC, subcutaneous.