EFFICACY, SAFETY, AND PHARMACOKINETICS OF ANTI-CD40 ANTIBODY ABIPRUBART (KPL-404) IN PATIENTS WITH RHEUMATOID ARTHRITIS: A PHASE 2, RANDOMIZED, PLACEBO-CONTROLLED, 12-WEEK-TREATMENT, PROOF-OF-CONCEPT STUDY

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Disclosures

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Elsa Van Duuren: speakers bureau for Pfizer, Aspen, Janssen, Lilly, Adcock-Ingram, Roche, Mundi-Pharma, AbbVie; consultant for Boehringer-Ingelheim, AbbVie, Aspen, Pfizer, Janssen.

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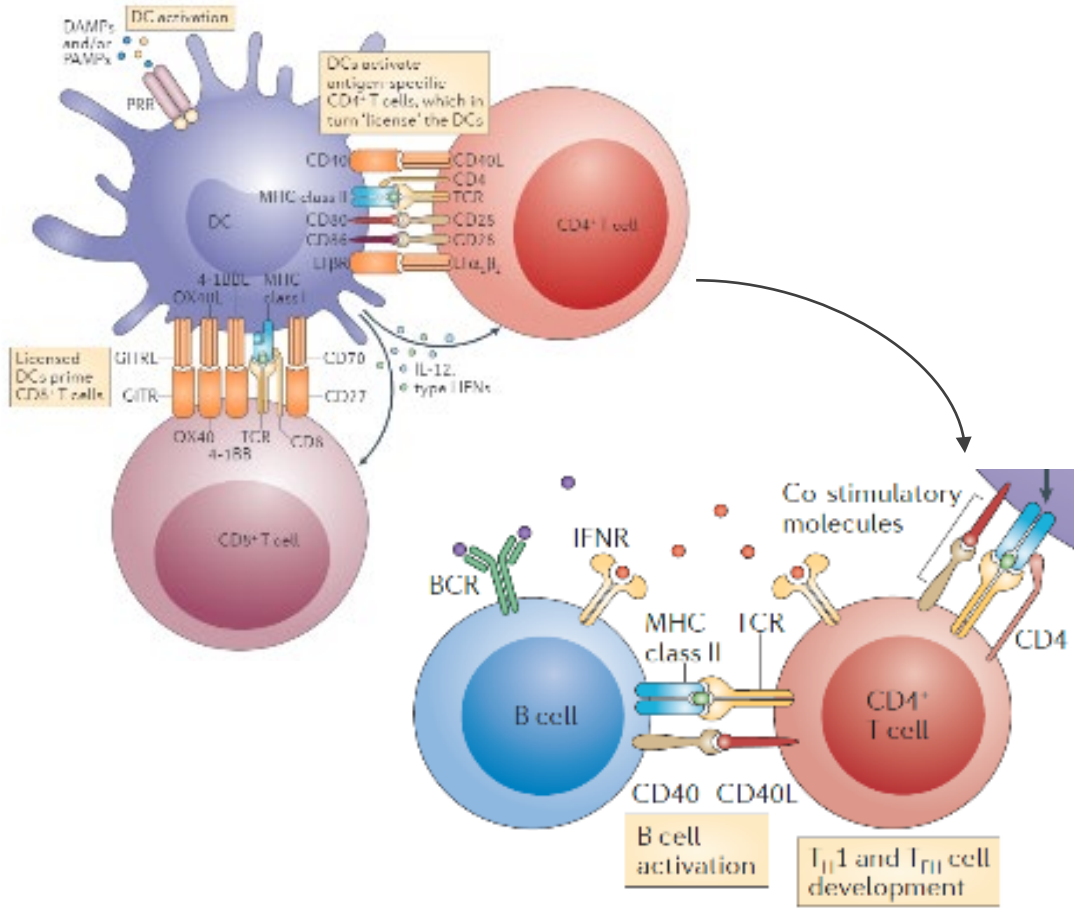
CD40/CD154 Interaction: Essential Immune Pathway for T-Cell Priming and T-Cell Dependent B-Cell Responses

- 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



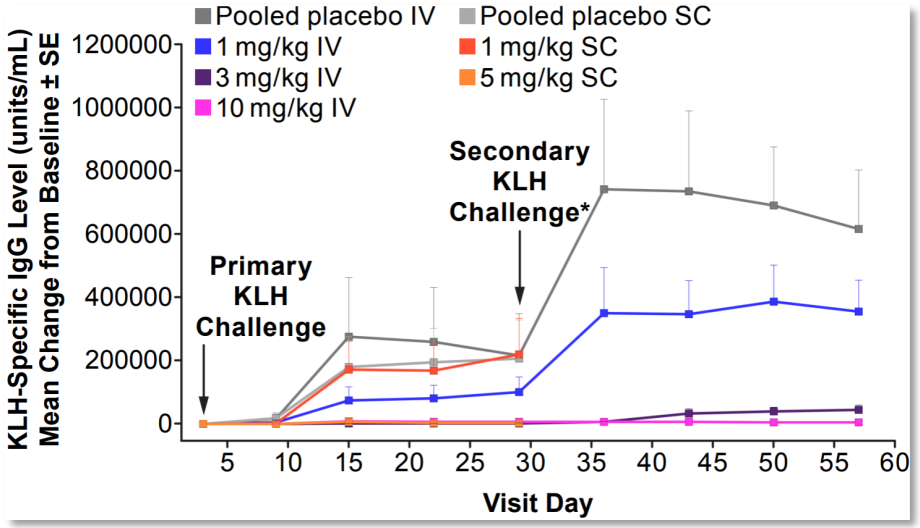
Unmet Need: Limited treatment options for patients with rheumatoid arthritis (RA) who have had inadequate response to or are intolerant of currently-available biologics or targeted synthetic DMARDs.

Figures adapted by permission from: Springer Nat Rev: Immunol. Fine-tuning of dendritic cell biology by the TNF superfamily, Summers deLuca L, Gommerman JL. Figure 1. 2012 and from: Springer Nat Rev: Immunol. Nucleic acid sensing at the interface between innate and adaptive immunity in vaccination, Desmet CJ, Ishii KJ. Figure 1. 2012.; DMARDs: disease-modifying anti-rheumatic drugs

Abiprubart Demonstrated Prolonged TDAR Suppression in Phase 1

- Phase 1 SAD study in healthy human volunteers[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 further investigation with chronic subcutaneous (SC) administration



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

1) Samant et al. JPET, 2023; TDAR: T-cell dependent antibody response; RA: rheumatoid arthritis; SAD: single ascending dose; SC: subcutaneous

Phase 2 Trial of Abiprubart in Rheumatoid Arthritis

Phase 2 Study Objectives:

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

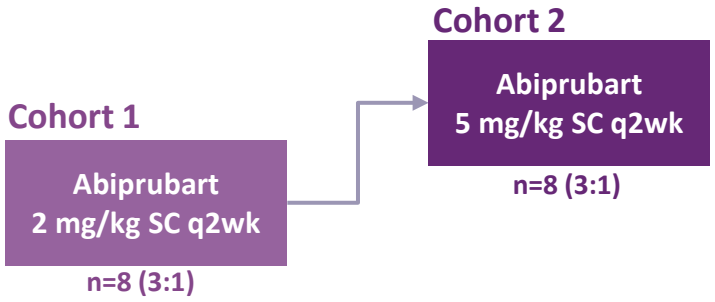
PATIENT POPULATION:

- 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.

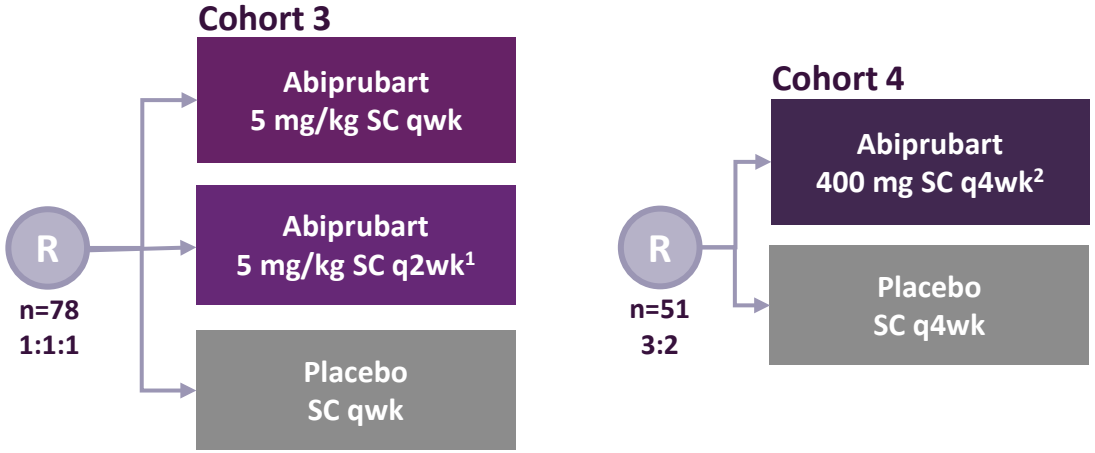
PHARMACOKINETICS (PK) LEAD-IN



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

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
SC = subcutaneous; qwk = every week; q2wk = every other week; q4wk = every four weeks; AUC = Area Under the Curve; RF = Rheumatoid Factor; ACPA = anti-citrullinated protein antibodies, PD = Pharmacodynamics; PK = Pharmacokinetics; R = Randomization; bDMARDs: biological disease-modifying anti-rheumatic drugs; JAKi: Janus kinase inhibitor; hsCRP: high sensitivity c-reactive protein

Baseline Demographics And Disease Characteristics Balanced Across Treatment Arms

	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 (9.4)	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)
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 (191.52)	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)

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); SD: standard deviation; RA: rheumatoid arthritis; Data are presented as mean (standard deviation) or percentage (n = number of patients)

Phase 2 Trial of Abiprubart in RA Met Primary Efficacy Endpoint

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

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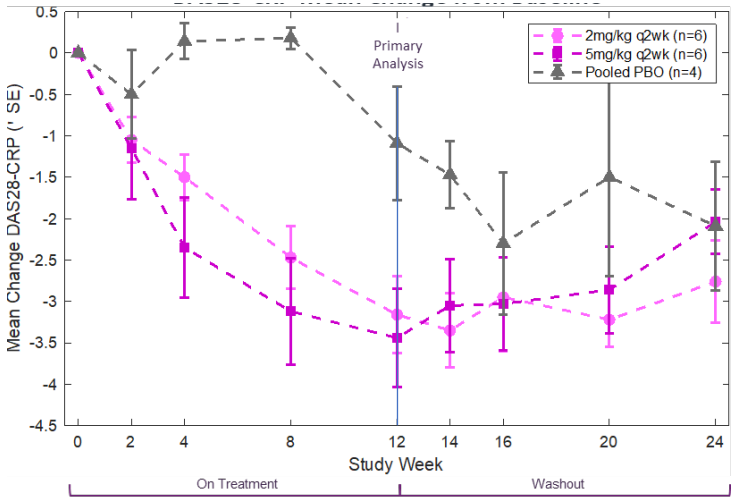
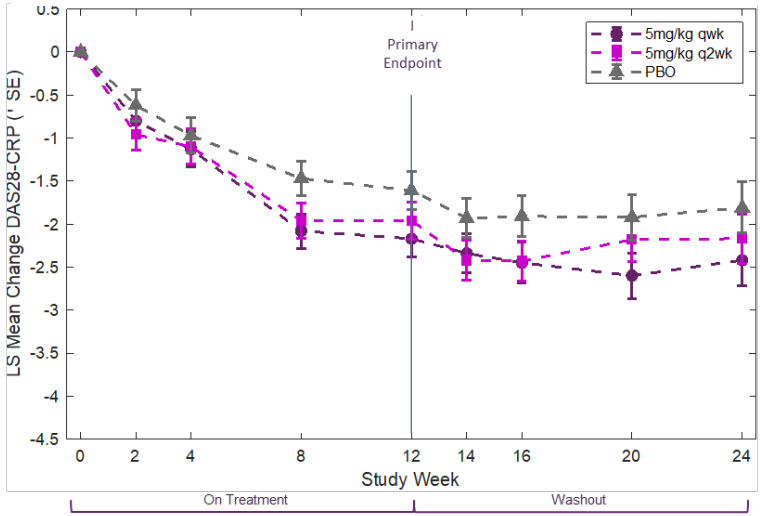
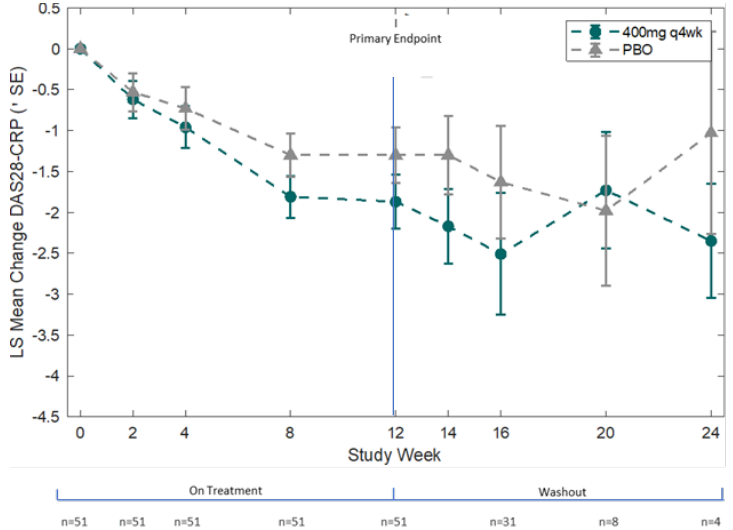
Cohort 1 & 2
DAS28-CRP Mean Change from Baseline[1*]



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



Cohort 4
DAS28-CRP LS Mean Change from Baseline[3*]



Primary Efficacy Results at Week 12

Cohort 1: 2 mg/kg SC q2wk
Mean Difference: -2.07, p=0.0312
- Abiprubart (n=6): -3.16
- Pooled Placebo (n=4): -1.09

Cohort 2: 5 mg/kg SC q2wk
Mean Difference: -2.35, p=0.0338
- Abiprubart (n=6): -3.44
- Pooled Placebo (n=4): -1.09

Cohort 3: 5 mg/kg SC qwk
LS Mean Difference: -0.57, p=0.0470
- 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=0.2124
- 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]

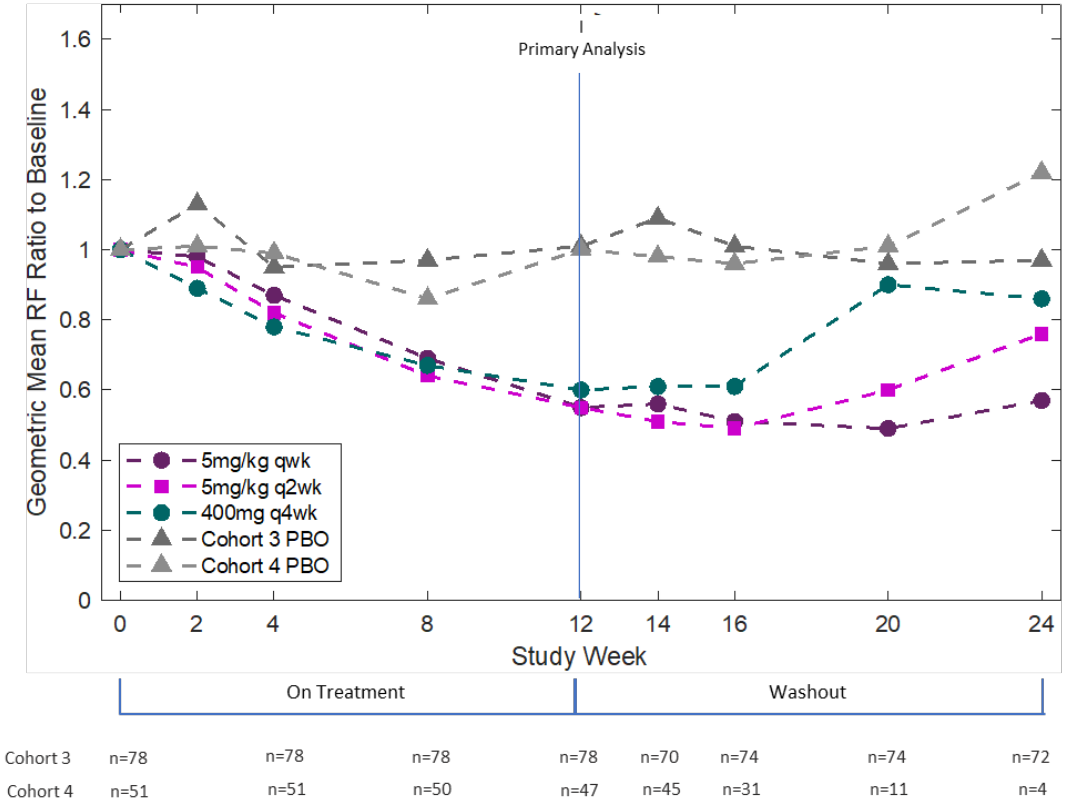
1) Final data; 2) Modified Intention to Treat (mITT) analysis population (all randomized subjects who received at least one dose of study drug and had a baseline assessment and at least one post-baseline assessment for the primary efficacy endpoint); 3) Topline data; Modified Intention to Treat (mITT) 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); the Phase 2 study of abiprubart in rheumatoid arthritis is ongoing, this topline analysis includes all patients having reached Week 12, and follow-up to Week 24 is ongoing; *Data cutoff: 29-Feb-2024

DAS28-CRP = Disease Activity Score of 28 Joints Using C-reactive Protein; SC = Subcutaneous; LS = Least Squares; CI = Confidence Interval; RA: rheumatoid arthritis

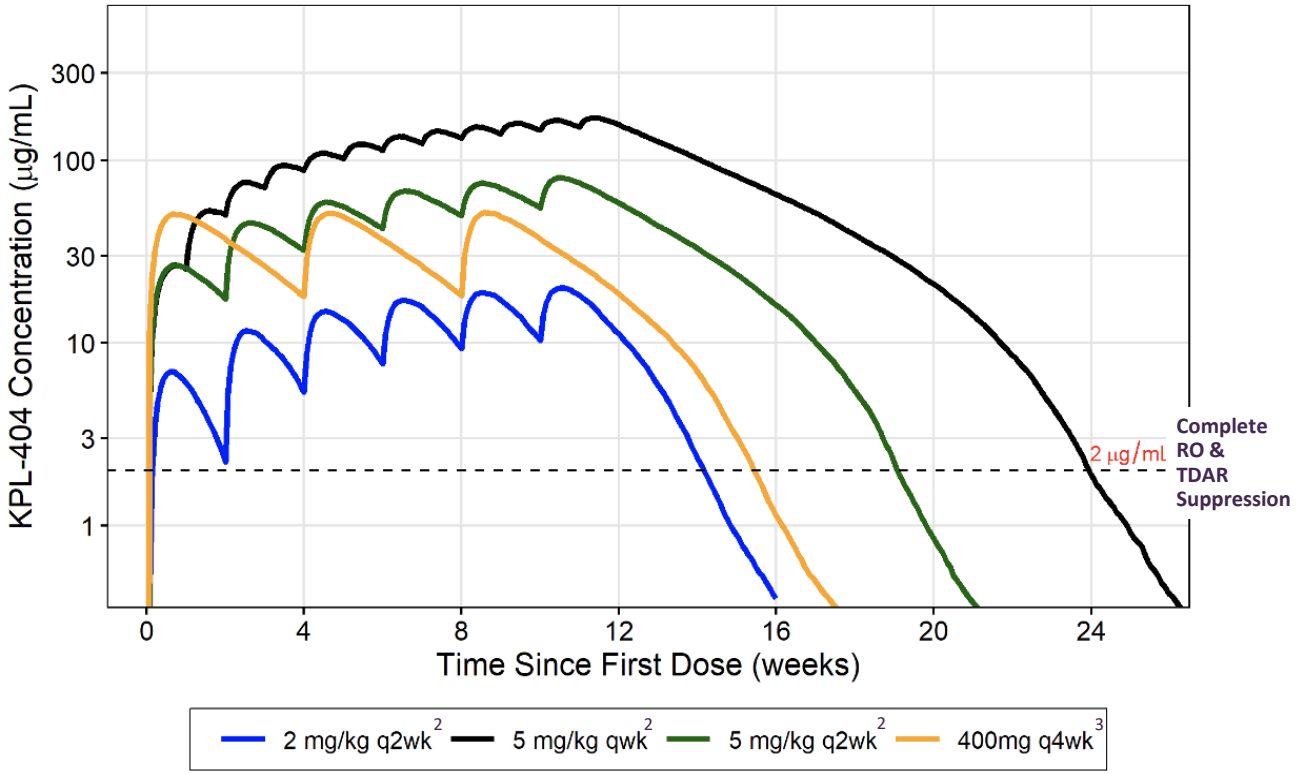
Pharmacodynamics & Pharmacokinetics: Statistically Significant Similar Magnitude Reductions in Rheumatoid Factor at all SC Dose Intervals

RF is an anti-Ig Fc 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*]



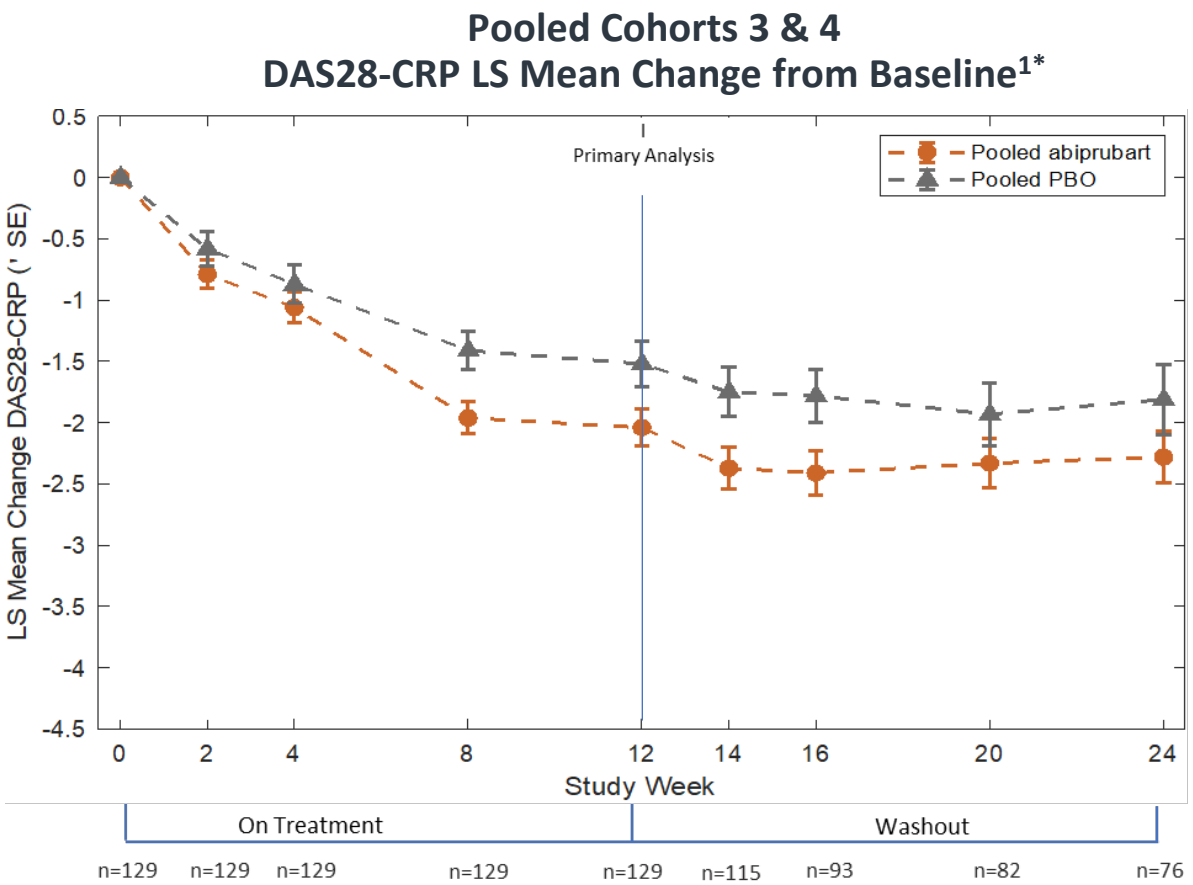
PK Modeling Data[4*]: Full Target Engagement from 5 mg/kg SC Weekly to 400 mg SC Monthly Dosing



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 are 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

*Data cutoff: 29-Feb-2024; PK: pharmacokinetics; RO = receptor occupancy; TDAR = T-cell dependent antibody response; RA: rheumatoid arthritis; SC: subcutaneous

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);
*Data cutoff: 29-Feb-2024

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)	25.8 (n=8)	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)	25.8 (n=8)	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)	12.9 (n=4)	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	3.8 (n=1)	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	0	4.0 (n=1)	0	0	0
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; *Data cutoff: 29-Feb-2024

Summary and Conclusions

- **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 compared to 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.**

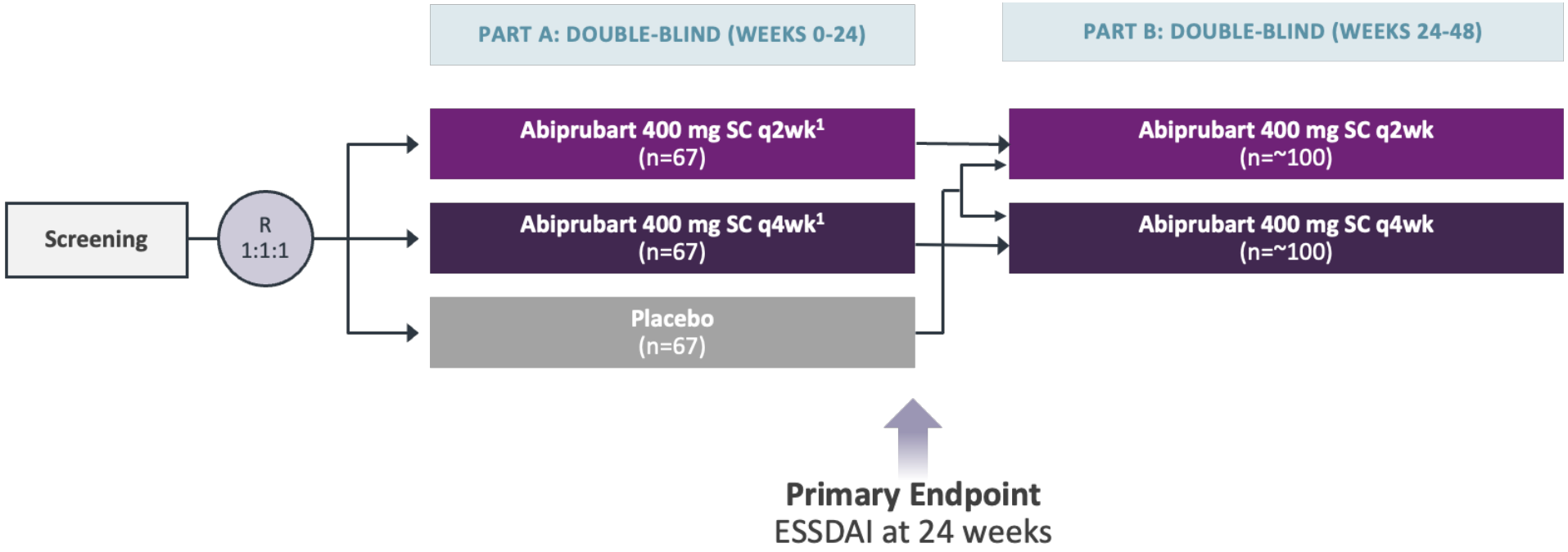
RA: rheumatoid arthritis; RF: rheumatoid factor

Impact on Clinical Practice

Abiprubart has potential to provide meaningful benefit to patients suffering from a spectrum of autoimmune diseases, including Sjögren's Disease, a debilitating disease with no current FDA-approved therapies.

Phase 2b Sjögren's Disease Trial Study Design

Trial is expected to initiate in the second half of 2024



1) All dose levels are subcutaneous; 2) Both abiprubart dose levels include an 800mg loading dose on Day 1; RO = receptor occupancy; TDAR = T-Cell Dependent Antibody Response; PK: pharmacokinetics

Acknowledgments

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