Safety, Tolerability, and Activity of JNJ-67484703 in Participants with Active Rheumatoid Arthritis: Results of a Multicenter, Double-Blind, Placebo-Controlled, Randomized, Multiple-Dose Phase 1b Study

Irving TC Ling[2], Stanley J Marciniak [1], Stephen H Clarke[3], Vani Lakshminarayanan[4], Matthew J Loza [4], Sophia G Liva[5], Tong Wang[6], Ashley Orillion[4], Ilia Tikhonov[7], Erika H Noss[1]

[1]Johnson & Johnson, Translational Medicine, Spring House, PA, USA; [2]Johnson & Johnson, Translational Medicine, Cambridge, MA, USA; [3]Johnson & Johnson, Translational Science, Cambridge, MA, USA; [4]Johnson & Johnson, Translational Science, Spring House, PA, USA; [5]Johnson & Johnson, Clinical Pharmacology, Spring House, PA, USA; [6]Johnson & Johnson, Biostatistics, Spring House, PA, USA; [7]Johnson & Johnson, Medical Safety, Spring House, PA, USA

Johnson & Johnson

Abstract

Background: Programmed cell death protein-1 (PD1) is an inhibitory receptor predominantly expressed on T cells, particularly on chronically activated effector and follicular helper/peripheral helper T cells. PD-1 antagonizing therapeutic antibodies in cancer therapy release an immune break, potentially leading to immune-related adverse events, including colitis and arthritis, in a subset of patients. Rheumatoid arthritis (RA) is characterized by marked PD1+ T cell infiltration into inflamed synovium, suggesting dysregulated PD-1 activity contributes to disease pathogenesis. JNJ-67484703 is a humanized IgG1κ antibody that agonizes and depletes PD1+ T cells, potentially reducing aberrant inflammatory responses in autoimmune conditions.

Objectives: To evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy of JNJ-67484703 following multiple subcutaneous administrations in participants with active RA.

Methods: This was a Phase 1, randomized, double-blind, placebo-controlled, multiple-dose, multi-center study of approximately 30 weeks in duration, with a screening visit within 6 weeks prior to study drug intervention, 10 weeks of study treatment (at Weeks 0, 1, 2, 4, 6, 8, and 10), and 14 weeks of follow-up. Participants with active RA were randomly assigned to receive JNJ-67484703 2 mg/kg or placebo subcutaneously in a 5:1 ratio for the first 6 patients. Safety was assessed through Day 29, and it was determined that enrollment would proceed to the 3 mg/kg dose level. Cumulative safety and tolerability were assessed through Day 29 for the next 6 patients in a 5:1 ratio. The remaining 32 patients were enrolled to achieve an overall 2:1 JNJ-67484703 3 mg/ kg:placebo ratio to assess efficacy. Key eligibility criteria were as follows: age 18-65 years at enrollment, diagnosis of RA for >6 months based on American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria (2010), rheumatoid factor or anti-cyclic citrullinated peptide antibody positive, ≥6 swollen and ≥6 tender joint counts (screening and Day -1), reactive C protein (CRP) ≥0.3 mg/dL (screening). Participants were also required to have an inadequate response to ≥12 weeks of conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) and maintain stable doses of >1 csDMARDs during the study. Stable doses of non-steroidal anti-inflammatory drugs and oral glucocorticoids < 10 mg prednisone equivalent were also permitted. The primary objective to characterize the safety and tolerability of JNJ-67484703 was assessed by number of treatment-emergent adverse events (TEAEs) and other safety measures. Key secondary objectives of PK, immunogenicity, PD, and efficacy of JNJ-67484703 were also measured.

Results: Of 92 patients screened, 44 patients were randomized to JNJ-67484703 2 mg/kg (n=5), 3 mg/kg (n=25) or placebo (n=14). Demographics and baseline characteristics were comparable across the JNJ-67484073 and placebo groups, with a median age of 55.5 years, disease duration of 8.7 years, and baseline DAS-28-CRP of 6.3. All patients were receiving methotrexate, 72.7% were receiving oral glucocorticoids, and 40.9% were receiving NSAIDs. No participants had prior exposure to biologic or targeted-synthetic DMARDs. TEAEs were reported in 4 (80%) patients receiving JNJ-4703 2 mg/kg, 17 (68%) patients receiving JNJ-4703 3 mg/kg, and 10 (71%) patients receiving placebo. None of the reported TEAEs were severe in intensity, and no deaths were reported during the study. Three serious TEAEs were reported in 2 participants: SARS-COV-2 infection followed by pneumonia in 1 participant (2 mg/kg group) and community-acquired pneumonia in 1 participant (3 mg/kg group). Infections occurred in approximately 20% of patients in each treatment group, with urinary tract infections (UTIs) the most common (7.1% placebo, 10% combined JNJ-67484703 group). All patients who developed UTIs had a history of recurrent UTIs and no clinical signs of active infection at enrollment. At Week 12, the least squares (LS) mean difference (95% confidence interval (CI)) in Week 12 DAS28-CRP from baseline between the JNJ-67484703 3 mg/kg and placebo groups was -0.69 (-1.55, 0.18); nominal p=0.117. At the end of follow-up (Week 24), both JNJ-67484703 groups continued to show numerically greater reductions in DAS28-CRP versus placebo, but the magnitude of the difference decreased; the LS mean difference (95% CI) between JNJ-67484703 3 mg/kg and placebo was -0.35 (-1.01, 0.32) with nominal p=0.295. At Week 12, the proportions of patients achieving ACR20, ACR50, and ACR70 were generally comparable across treatment groups, but analysis by visit showed numerically greater ACR20 responses in the JNJ-67484703 3 mg/kg group versus placebo between Week 4 and Week 10. JNJ-67484703 induced a decrease in circulating PD-1+ CD4+ and CD8+ T cells that was dependent on the cell surface density of PD-1 expression. Steady state serum concentrations of JNJ-67484703 were approximately achieved by Week 4, and overall incidence of antibodies to JNJ-67484703 was low.

Conclusions: Overall, administration of JNJ-67484703 at 2 mg/kg and 3 mg/kg through 10 weeks was safe and well-tolerated. Numerically greater improvement in Week 12 DAS28-CRP from baseline was observed in the 3 mg/kg group compared to placebo. Participants treated with JNJ-67484703 showed a selective decrease in circulating PD-1+ T cells. The overall incidence of antibodies to JNJ-67484703 was low.

Disclosures: Authors are current or former employees of Johnson & Johnson and may own stock in Johnson & Johnson

Rationale

- Programmed cell death (PD-1) protein-1 is an inhibitory receptor expressed predominantly by T cells and PD-1 ligand engagement suppresses T cell function
- High PD-1 expression is found on chronically activated effector T cells and on follicular helper/peripheral helper CD4$^+$ T cells that assist in antibody production
- In RA synovium, an overabundance of PD-1$^+$ cells suggests down-regulation of PD-1 ligands with decreased pathway activity contributing to pathology
- JNJ-67484703 is a humanized IgG1κ antibody that depletes or agonizes PD-1$^+$ cells to restore immune homeostasis

Objective

Evaluate safety, tolerability, pharmacokinetics (PK), pharmaco-dynamics (PD), and efficacy of JNJ-67484703 following multiple subcutaneous administrations in participants with active RA.

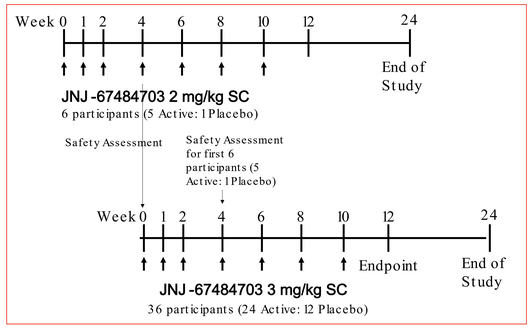
Conclusions

The PD-1 agonist JNJ-67484703 in RA patients

- Was generally safe and well-tolerated after 10 weeks of dosing
- Showed evidence for efficacy over placebo
- Exhibited selective depletion of PD-1-expressing T cells
- Showed low incidence of anti-drug antibodies

Methods

Figure 1. Schema of the JNJ-67484703 Phase 1b study in participants with active RA



Key Eligibility Criteria

- 18-65 years of age
- *At screening:* RA diagnosis by ACR/EULAR 2010 criteria for ≥6 months; C-reactive protein ≥0.3 mg/dL; RF or ACPA positive
- *At screening and Day 1:* ≥6 tender and swollen joints
- Inadequate response to ≥12 weeks of csDMARD therapy and continued ≥1 csDMARDs during the study (exposure to ≤2 b/tsDMARDs allowed by protocol amendment)
- Treatment with steroids (≤10 mg/day prednisone equivalent) and NSAID at stable doses permitted

Sample Size Calculation

- At least 30 participants (2 active:1 placebo) provide ≥80% power using 2-sided t-test at α=0.2 to detect a -1 difference between treatment and placebo in the change in DAS28-CRP change at Week 12 from baseline

Results

Table 1. Treatment Disposition

	Placebo	JNJ-67484703 2 mg/kg	JNJ-67484703 3 mg/kg	Total
Full Analysis Set	14	5	25	44
Discontinued Study Treatment Prior to Week 10	1 (7.1%)	1 (20.0%)	3 (12.0%)	5 (11.4%)
Reason for Discontinuations				
Adverse Events	0	1	1	2
Withdrawal by Subject*	0	0	1	1
Other*	1	0	1	2

*2 personal reasons, 1 left the country

Table 2. Demographics and Baseline Characteristics

Characteristic*	Placebo (n=14)	JNJ-67484703 2 mg/kg (n=5)	JNJ-67484703 3 mg/kg (n=25)
Age, years	53.5 (33–65)	56.0 (36–64)	55.0 (22–65)
Female, n (%)	12 (85.7)	4 (80.0)	21 (84.0)
White, n (%)	14 (100.0)	5 (100.0)	24 (96.0)
Hispanic/Latino, n (%)	0	0	1 (4.0)
BMI, kg/m^2	26.3 (20–32)	26.8 (22–32)	27.3 (21–39)
Disease duration, years	6.5 (1–27)	12.7 (3–21)	5.5 (1–28)
Anti-CCP positive, n (%)	12 (85.7)	5 (100.0)	25 (100.0)
RF positive, n (%)	14 (100.0)	5 (100.0)	23 (92.0)
DAS28-CRP (mg/L)	6.3 (4–7)	6.1 (5–7)	6.3 (5–8)
Tender joint count	34.5 (6–67)	43.0 (8–45)	39.0 (12–68)
Swollen joint count	23.5 (6–48)	16.0 (7–23)	25.0 (8–44)
CRP, median (range), mg/dL	0.7 (0–6)	1.8 (1–2)	1.1 (0–6)

*Unless otherwise indicated, values presented are median (range).

Table 2. Demographics and Baseline Characteristics *(continued)*

Characteristic*	Placebo (n=14)	JNJ-67484703 2 mg/kg (n=5)	JNJ-67484703 3 mg/kg (n=25)
Patient's global disease activity (VAS 0–10)	7.0 (7–9)	6.0 (4–7)	7.0 (4–9)
Physician's global disease activity (VAS 0–10)	7.0 (3–10)	7.0 (3–7)	7.0 (3–10)
HAQ disability index (0–3)	1.9 (0–3)	1.3 (1–2)	1.6 (0–3)
Baseline RA medication use n (%)			
csDMARDs	14 (100.0)	5 (100.0)	25 (100.0)
Methotrexate	14 (100.0)	5 (100.0)	25 (100.0)
Sulfasalazine	0	0	1 (4.0)
Anti-malarials	0	0	1 (4.0)
Oral corticosteroids	9 (64.3)	2 (40.0)	21 (84.0)
NSAIDs	5 (35.7)	3 (60.0)	10 (40.0)

*Unless otherwise indicated, values presented are median (range).

Table 3. Summary of Treatment -Emergent Adverse Events (TEAEs) through Week 24 *(Primary Objective)*

	Placebo (n=14)	JNJ-67484703 SC 2 mg/kg (n=5)	JNJ-67484703 SC 3 mg/kg (n=25)	JNJ-67484703 SC Combined (n=30)
Follow-up Duration, mean, days	170.8	165.4	164.0	164.2
Exposure, mean, days	69.4	68.0	68.6	68.5
Participants with ≥1 TEAE, n (%)	10 (71.4)	4 (80.0)	17 (68.0)	21 (70.0)
Serious TEAEs	0	1 (20.0)*	1 (4.0)**	2 (6.7)
TEAEs leading to study treatment discontinuation	0	1 (20.0)	1 (4.0)	2 (6.7)
TEAEs leading to death	0	0	0	0
TEAEs in >2 participants				
Anemia***	0	0	4 (16.0)	4 (13.3)
CMV test positive	2 (14.3)	1 (20.0)	2 (8.0)	3 (10.0)
EBV test positive	4 (28.6)	1 (20.0)	4 (16.0)	5 (16.7)
UTI	1 (7.1)	0	3 (12.0)	3 (10.0)
TEAE of infection	3 (21.4)	1 (20.0)	5 (20.0)	6 (20.0)
Injection site reactions	0	0	0	0
Hypersensitivity reactions	0	0	0	0

*COVID-19 infection followed by pneumonia, **Community-acquired pneumonia, ***Review laboratory results showed participants had low levels at baseline that improved on study treatment or were isolated findings.

Figure 2. (A) Change from Baseline in DAS28-CRP, (B) Change from Baseline in CDAI, and (C) ACR20 response through Week 12 *(treatment failure rules applied)*

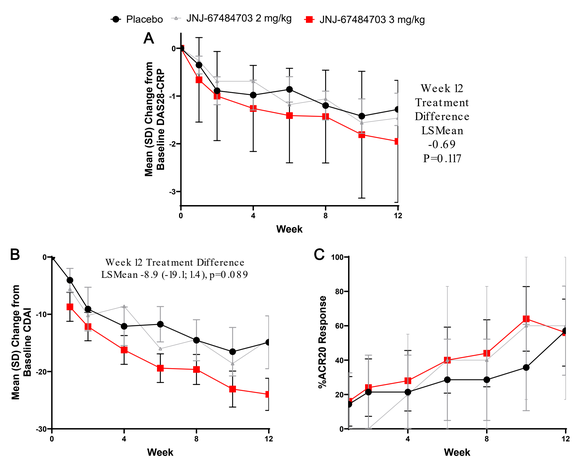


Table 4. Efficacy Endpoints at Week 12

Efficacy Endpoint Week 12	Placebo (n=14)	JNJ-67484703 2 mg/kg (n=5)	JNJ-67484703 3 mg/kg (n=25)
Response evaluable (n)	14	4	25
DAS28-CRP change from baseline, LS mean (95% CI)	-1.27 (-1.96, -0.58)	-1.62 (-2.84, -0.41)	-1.96* (-2.48, -1.44)
ACR20, n (%)	8 (57.1)	3 (60.0)	14 (56.0)
ACR50, n (%)	3 (21.4)	1 (20.0)	5 (20.0)
ACR70, n (%)	2 (14.3)	0	3 (12.0)
DAS28-CRP remission, n (%)	2 (14.3)	0	3 (12.0)
DAS28-CRP low disease activity, n (%)	2 (14.3)	0	7 (28.0)
CDAI, change from baseline score, LS mean (95% CI)	-14.96 (-23.13, -6.79)	-14.93 (-28.88, -0.97)	-23.83** (-29.99, -17.66)
ACR component scores, mean (SD) change from baseline			
Tender joint count	-12.15 (15.16)	-11.60 (9.40)	-20.94 (18.75)
Swollen joint count	-8.03 (11.68)	-6.60 (6.19)	-13.91 (9.97)
Physician's Global Assessment of Disease Activity	-1.93 (2.46)	-1.80 (2.05)	-2.60 (2.02)
CRP	-0.23 (1.61)	-0.88 (0.93)	-0.84 (1.50)
Patient's Global Assessment of Disease Activity	-2.50 (1.99)	-2.00 (2.12)	-2.40 (2.20)
Patient's Assessment of Pain	-2.64 (2.31)	-2.20 (1.64)	-1.96 (1.99)
HAQ-DI	-0.56 (0.48)	-0.43 (0.48)	-0.57 (0.45)

*nominal p=0.117, **nominal p=0.089

Figure 3. Median Time-Profile of Ratio to Baseline of (A) PD-1^{hi}, (B) PD-1^{lo}, and (C) PD-1^{neg} CD4+ T cells

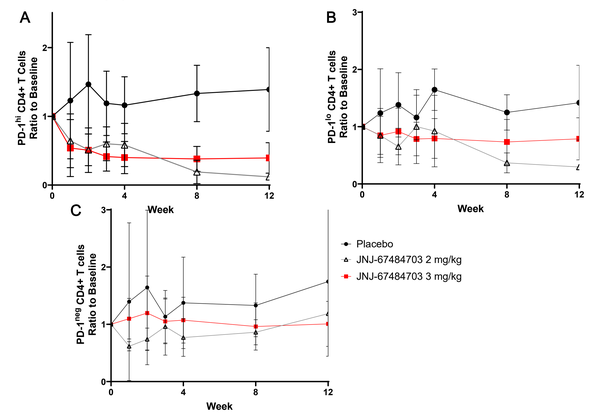


Table 5. Immunogenicity Analysis through Week 24

	JNJ-67484703 2 mg/kg	JNJ-67484703 3 mg/kg
Analysis Set	5	25
Participants positive for antibodies to JNJ-67484703 at baseline	1 (20.0%)	3 (12.0%)
Participants positive for treatment-boosted antibodies to JNJ67484703	0	0
Participants positive for treatment-emergent antibodies to JNJ-67484703	0	2 (8.0%)

Acknowledgments We would like to thank all investigators who were part of these study. We would also like to thank Erin Doyle, PhD, (J&J Translational Sciences) for support with sample evaluation and data analysis.

Scan the QR code.
The QR code is intended to provide scientific information for the individual reference, and the information should not be altered or reproduced in anyway.
https://www.congresshub.com/Immunology/EULAR2025/RheumatologyEarlyAssets/Noss