Name of Sponsor/Company: Astellas Pharma Inc.		
Name of Finished Product: Not available		
Name of Active Ingredient: ASP5094		

SYNOPSIS

Title of Study: Phase 2a Study of ASP5094, Protocol Number 5094-CL-0201

- A Phase 2a, Randomized, Placebo-controlled, Double-blind, Parallel-group Study to Evaluate the Efficacy and Safety of ASP5094 in Patients With Rheumatoid Arthritis on Methotrexate -

Investigators/Coordinating Investigator: [redacted]

Study Center(s): 31 sites in Japan

Publication Based on the Study: No publications based on the results of this study were available at the time this report was approved.

Study Period:

Study Initiation Date (Date of First Informed Consent): 29 Sep 2017

Study Completion Date (Date of Last Evaluation): 16 Oct 2018

Phase of Development: Phase 2a

Objectives: The objective of this study was to evaluate the efficacy, safety, and pharmacokinetics of ASP5094 (10 mg/kg) in subjects with rheumatoid arthritis (RA) on methotrexate (MTX).

Methodology: This clinical study was a multicenter, randomized, placebo-controlled, double-blind, parallel-group study to evaluate the efficacy, safety, and pharmacokinetics of ASP5094 (10 mg/kg) used in combination with MTX in subjects who had moderate to severe active RA despite using MTX. Subjects were randomized to ASP5094 or placebo in a 1:1 ratio at baseline after the screening period. During the study, the study drug was intravenously administered every 4 weeks for a total of 3 times (day 1, week 4, and week 8).

Number of Subjects (Planned, Enrolled, and Analyzed): The number of subjects planned for the study was a total of 60 subjects (ASP5094 group: 30 subjects, placebo group: 30 subjects). A total of 66 subjects were randomized (ASP5094: 33 subjects, placebo: 33 subjects), and 59 subjects completed the study (ASP5094: 27 subjects, placebo: 32 subjects).

Diagnosis and Main Criteria for Inclusion: Subjects who were candidates for participation in the study were screened for the inclusion/exclusion criteria before enrollment into the study.

Inclusion:

1. Institutional Review Board-approved written informed consent must have been obtained from the subject prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject of either sex who was ≥ 20 years of age at the time of informed consent.

3. Subject had RA diagnosed according to the 1987 American College of Rheumatology (ACR) criteria or the 2010 ACR/European League Against Rheumatism (EULAR) criteria at least 6 months prior to screening.
4. Subject met the 1991 ACR Revised Criteria for the Classification of Global Functional Status in RA Class I, II, or III at screening.
5. At screening and baseline, subject had active RA as evidenced by both of the following:
   a. ≥ 6 tender joints (using 68-joint assessment)
   b. ≥ 6 swollen joints (using 66-joint assessment)
6. Subject had a C-reactive protein (CRP) level (latex agglutination method) of > 0.50 mg/dL at screening.
7. Subject had continuously received MTX for at least 90 days prior to screening and was able to continue a stable dose of MTX from at least 28 days prior to screening throughout the study period.
8. Female subjects had to be either:
   - Of nonchildbearing potential:
     - Postmenopausal (defined as at least 1 year without any menses) prior to screening or documented surgically sterile (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy).
   - Or, if of childbearing potential:
     - Agree not to try to become pregnant during the study and for 120 days after the final study drug administration.
     - Had a negative urine pregnancy test at screening and baseline.
     - If heterosexually active, agree to consistently use 1 form of highly effective birth control† throughout the study period and for 120 days after the final study drug administration. (Unless the partner had undergone a vasectomy‡ or was sterile due to a bilateral orchiectomy.)
9. Female subject must have agreed not to breastfeed throughout the study period and for 120 days after the final study drug administration.
10. Female subject must not have donated ova throughout the study period and for 120 days after the final study drug administration
11. A sexually active male subject with female partner(s) who were of childbearing potential was eligible if the subject:
    - Agreed to use a male condom throughout the study period and for 120 days after the final study drug administration.
    - Had not had a vasectomy‡ or was not sterile due to a bilateral orchiectomy, but his female partner was utilizing 1 form of highly effective birth control† throughout the study period.
12. Male subject must not have donated sperm throughout the study period and for 120 days after the final study drug administration.
13. Male subject with a pregnant or breastfeeding partner must have agreed to remain abstinent or use a condom for the duration of the pregnancy or time the partner was breastfeeding throughout the study period and for 120 days after the final study drug administration.
14. Subject must have agreed not to participate in another interventional study during the present study.

† Highly effective forms of birth control included the following:

- Consistent and correct usage of established hormonal contraceptives that inhibited ovulation
- Established intrauterine device or intrauterine system

‡ Vasectomy: It was considered a highly effective contraception method, provided that the absence of sperm had been confirmed. If not, an additional highly effective method of contraception was used.

Exclusion:

1. Subject had deviated from the criteria for previous and concomitant treatment (medication and nonmedication therapy) before baseline.
2. Subject had an ongoing infection that required antibiotics.
3. Subject was determined to be an inadequate responder to prior biologic disease-modifying antirheumatic drugs or janus kinase inhibitors by the investigator/subinvestigator.
4. Subject had participated in a previous ASP5094 clinical study.
5. Subject had participated in a clinical study or postmarketing clinical study of another ethical drug or medical device within 12 weeks (84 days).
6. Subject had an inflammatory arthritis other than RA (e.g., psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, sarcoidosis, gouty arthritis) or any other articular symptom that may have affected on joint assessment.
7. Subject met any of the following criteria for laboratory values at screening:
   - White blood cell count less than the lower limit of normal
   - Platelet count < 100000/μL
   - Alanine aminotransferase ≥ 2 times the upper limit of normal (ULN)
   - Aspartate aminotransferase ≥ 2 times the ULN
   - Total bilirubin ≥ 1.5 times the ULN
   - Positive serology test for hepatitis B surface antigen, hepatitis B virus DNA quantitation, or hepatitis C virus antibody
8. Subject had a positive T-SPOT or QuantiFERON Gold test within 90 days prior to screening or at screening. (When the result was equivocal or invalid, retest that included other test methods was allowed. If a retest was not performed, the criteria for positive results were followed.)
9. Subject had a history of or concurrent malignant tumor.
10. Subject had an autoimmune disease except for RA (excluding Sjogren's syndrome and chronic thyroiditis) or any severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiac, neurological, or mental illness.
11. Subject had a history of clinically significant allergy. (Clinically significant allergy was defined as specific antigen- or drug-induced allergy associated with systemic urticaria, anaphylaxis, and/or shock that required hospitalization.)
12. Subject had clinically significant abnormalities on 12-lead electrocardiogram (ECG) at screening.
13. Subject had a history of human immunodeficiency virus infection.
14. Subject had surgery or had a planned elective surgery (including oral surgery) within 30 days prior to screening throughout the study period and 120 days after the last study drug administration.
15. Subject had a wound that was currently healing (excluding wounds that did not require surgical/medical intervention) at baseline.
16. Subject was an employee of the Astellas group, study-related contract research organization, site management organization, or investigational site.
17. Subject had any condition that, in the opinion of the investigator/subinvestigator, made the subject unsuitable for study participation.

Waivers to the exclusion criteria were NOT allowed.

Test Product, Dose and Mode of Administration, Batch Numbers: ASP5094 10 mg/kg, intravenous infusion for about a 30-minute period, lot numbers: [redacted], [redacted]

Duration of Treatment (or Duration of Study, if applicable): Intravenous ASP5094 every 4 weeks for a total of 3 times (day 1, week 4, and week 8).

Reference Product, Dose and Mode of Administration, Batch Numbers: Since this study was a multicenter, randomized, placebo-controlled, double-blind, parallel-group study to evaluate the efficacy and safety of ASP5094 used in combination with MTX, the plastic bottles prepared for both ASP5094 and placebo were covered with aluminum foil or the like so as to be indistinguishable in appearance from each other when administered.

Placebo, intravenous infusion for about a 30-minute period, lot numbers: [redacted], [redacted]

Criteria for Evaluation: The primary and secondary efficacy endpoints in this study were as follows:

Primary efficacy endpoint:

- ACR50 response rate at Week 12

Secondary efficacy endpoint:

- ACR50 response rate at Weeks 1, 2, 4, 8, and 16

Secondary efficacy endpoints at Weeks 1, 2, 4, 8, 12, and 16 included the following:

- ACR20 response rate
- ACR70 response rate
- Change from baseline in the Disease Activity Score (DAS)28-CRP or DAS28-erythrocyte sedimentation rate (ESR) score
- Change from baseline in tender joint count (TJC) (68 joints)
- Change from baseline in swollen joint count (SJC) (66 joints)
- Percentage of subjects who had achieved a DAS28-CRP or DAS28-ESR score for remission (< 2.6)
- Percentage of subjects who had achieved a DAS28-CRP or DAS28-ESR score for low disease activity (≤ 3.2)
- Change from baseline in CRP and ESR
- Percentage of subjects who had achieved a good response according to the EULAR response criteria
- Percentage of subjects who had achieved a good or moderate response according to the EULAR response criteria
- Percentage of subjects who had achieved an ACR/EULAR score for remission. ACR/EULAR remission was defined as meeting all of the following 4 criteria:
  - TJC ≤ 1
  - SJC ≤ 1
  - CRP ≤ 1.0 mg/dL
  - Subject Global Assessment of Arthritis ≤ 10 mm (0- to 100-mm visual analog scale)
- Percentage of subjects who had achieved a Simplified Disease Activity Index (SDAI) score for remission (≤ 3.3)

- Percentage of subjects who had achieved a Clinical Disease Activity Index (CDAI) score for remission (≤ 2.8)
- Change from baseline in the Health Assessment Questionnaire - Disability Index

Pharmacokinetic variable: Serum concentrations of ASP5094

Pharmacodynamic variables: Tumor necrosis factor α, matrix metalloproteinase 3, interleukin-6, tenascin-C, vascular cell adhesion molecule-1, and OPN (full length and thrombin cleaved)

Safety variables: Adverse events, laboratory parameters, vital signs, body weight, and 12-lead ECG

Statistical Methods:

Efficacy:

For the analysis of primary endpoint, the ACR50-CRP response rates at week 12 were compared between the 2 treatment groups based on the full analysis set (FAS). For statistical comparison, Fisher's exact test was used, and the significance level was 10% (2-sided). The difference of the ACR50-CRP response rate between the 2 treatment groups and its 2-sided 90% confidence interval (based on the normal approximation) was also calculated.

For imputation of missing on ACR50-CRP response at week 12, a nonresponder imputation (NRI) method was used. A subject whose ACR response at week 12 was missing based on NRI was treated as a nonresponder.

Secondary endpoints were analyzed based on the FAS as follows:

- Binary variables were compared between the 2 treatment groups as in the primary analysis.
- Continuous variables (change from baseline) were compared using an analysis of covariance, with treatment group as the factor and baseline score as the covariate.

Pharmacokinetics/Pharmacodynamics:

For pharmacokinetic and pharmacodynamic parameters, descriptive statistics were presented.

Safety:

Adverse events: The number and percentage of subjects with treatment-emergent adverse events (TEAEs) and number of TEAEs, as classified by system organ class and preferred term (PT) coded using the MedDRA/Japanese version (MedDRA/J) Version 20.0, were summarized for safety analysis set (SAF). Summaries were provided for the following:

- The number and percentage of subjects with TEAEs
- The number and percentage of subjects with serious TEAEs
- The number and percentage of subjects with TEAEs leading to permanent discontinuation of study drug
- The number and percentage of subjects with drug-related TEAEs
- The number and percentage of subjects with TEAEs by severity

Laboratory parameters, vital signs, body weight, and 12-lead ECG: Observed values and changes from baseline at each scheduled visit were summarized using descriptive statistics or frequency tabulation.

Summary of Results/Conclusions:

Population:

A total of 91 subjects provided informed consent for this study. Of these, 66 subjects were enrolled and randomized to the placebo group (33 subjects) or the ASP5094 group (33 subjects).

Of the 66 randomized subjects, all were included in the SAF and the pharmacokinetic analysis set [Table 1]. The FAS consisted of 65 subjects (33 in the placebo group and 32 in the ASP5094 group). The per protocol set consisted of 60 subjects (33 in the placebo group and 27 in the ASP5094 group).

Of the 65 subjects in the FAS, 46 (70.8%) were female, and 19 (29.2%) were male. Age ranged from 30 to 77 years, body weight ranged from 37.9 to 100.8 kg, and the body mass index ranged from 15.2 to 34.6 kg/m^2 across the treatment groups [Table 2].

The mean (standard deviation [SD]) TJC (68 joints) in the placebo and ASP5094 groups was 12.3 (5.7) and 12.6 (5.1), respectively. The mean (SD) of the SJC (66 joints) was 11.2 (5.1) and 11.5 (4.6) in the placebo and ASP5094 groups, respectively. The mean (SD) of the DAS28-CRP was 4.98 (0.68) and 5.15 (0.61) in the placebo and ASP5094 groups, respectively.

The mean (SD) CRP was 1.406 (1.031) and 1.668 (1.418) mg/dL in the placebo and ASP5094 groups, respectively. The mean (SD) SDAI score was 28.90 (8.39) and 30.32 (8.21) in the placebo and ASP5094 groups, respectively. Other parameters such as TJC (28 joints), SJC (28 joints), and CDAI score showed approximately the same values in both treatment groups.

The mean duration of study drug exposure was 84.2 and 75.3 days in the placebo and ASP5094 groups, respectively. A total of 32 (97.0%) subjects in the placebo group and 27 (81.8%) subjects in the ASP5094 group were administered study drug for 65 or more days.

Efficacy/Pharmacokinetic/Pharmacodynamic Results:

Efficacy: Regarding the primary endpoint, the percentage of subjects achieving ACR50 response at Week 12 with NRI in the FAS, there was no statistically significant difference between the ASP5094 and placebo groups [Table 3]. A similar result was observed in the per-protocol set.

For the major secondary efficacy endpoints:

- Percentage of subjects achieving ACR50 response at each visit provided no statistically significant difference between the ASP5094 and placebo groups throughout the treatment period.
- Percentage of subjects achieving ACR20 response at each visit showed no statistically significant difference between the ASP5094and placebo groups.
- Percentage of subjects achieving ACR70 response at each visit provided no statistically significant difference between the treatment groups.
- Change from baseline in DAS28-CRP score at each visit provided no statistically significant difference between the treatment groups.
- DAS28-ESR score < 2.6 at each visit presented no statistically significant difference between the treatment groups.

Pharmacokinetics: Peak of mean serum ASP5094 concentration was achieved at the end of infusion. The mean serum ASP5094 concentrations corresponding to pre-dose apparently increased by time, suggesting that steady state of ASP5094 was not reached after 3 doses.

Pharmacodynamics: Overall, the change from baseline of the pharmacodynamic endpoints showed large variability, and there were no obvious differences in any of the ASP5094 treatment groups compared to the placebo treatment group.

Safety Results:

The proportion of subjects experiencing a TEAE was higher in the ASP5094 group than in the placebo group (60.6% [20/33] of subjects versus 39.4% [13/33] of subjects, respectively) [Table 4]. The common TEAEs (occurring in ≥ 10% of subjects in any treatment group) by PT were RA and viral upper respiratory tract infection [Table 5].

The proportion of subjects experiencing a drug-related TEAE was higher in the ASP5094 group than in the placebo group (15.2% and 6.1% of subjects, respectively) [Table 6].

No deaths were reported during the study.

Four serious TEAEs were observed in 2 subjects in the ASP5094 group and in 1 subject in the placebo group [Table 7]. The serious TEAEs of bronchitis and influenza occurring in 1 subject in the ASP5094 group were considered related to study drug.

A total of 2 TEAEs leading to permanent discontinuation were reported in subjects in the ASP5094 group. The TEAE of pneumonia was considered possibly related to study drug [Table 8].

No notable change was observed in any laboratory test parameter, vital sign, body weight, and 12-lead ECG.

CONCLUSIONS:

- ASP5094 in combination with MTX was not efficacious in the treatment of moderate to severe active RA.

Date of Report: 18-Mar-2019

Table 1 Analysis Sets

Population, n (%)	Placebo (N = 33)	ASP5094 (N = 33)	Total (N = 66)
Randomized	33 (100.0)	33 (100.0)	66 (100.0)
Subjects who took study drug	33 (100.0)	33 (100.0)	66 (100.0)
Full analysis set †	33 (100.0)	32 (97.0)	65 (98.5)
Per protocol set ‡	33 (100.0)	27 (81.8)	60 (90.9)
Safety analysis set §	33 (100.0)	33 (100.0)	66 (100.0)
Pharmacokinetic analysis set ¶	33 (100.0)	33 (100.0)	66 (100.0)
Pharmacodynamic analysis set ††	33 (100.0)	32 (97.0)	65 (98.5)

†: All subjects who were randomized and received at least 1 dose of study drug and had at least 1 efficacy measurement after study drug administration.
‡: All subjects in the full analysis set who met specific criteria (refer to protocol).
§: All subjects who received at least 1 dose of study drug.
¶: All subjects who received at least 1 dose of study drug and from whom at least 1 pharmacokinetic analysis sample was collected after the first dosing.
††: All subjects who received at least 1 dose of study drug and from whom at least 1 pharmacodynamic analysis sample was collected after the first dosing.
Source: Table 12.1.1.2

Table 2 Demographic Characteristics

Category Statistic	Placebo (N = 33)	ASP5094 (N = 32)	Total (N = 65)
Sex, n (%)			
Male	7 (21.2)	12 (37.5)	19 (29.2)
Female	26 (78.8)	20 (62.5)	46 (70.8)
Race, n (%)			
Asian	33 (100.0)	32 (100.0)	65 (100.0)
White	0	0	0
Black or African American	0	0	0
Other	0	0	0
Age group, years (%)			
< 65 years	24 (72.7)	23 (71.9)	47 (72.3)
≥ 65 years	9 (27.3)	9 (28.1)	18 (27.7)
Age, years			
n	33	32	65
Mean	57.9	54.8	56.3
SD	9.1	13.0	11.2
Median	57.0	55.5	56.0
Min, max	41, 77	30, 77	30, 77
Weight, kg			
n	33	32	65
Mean	57.82	62.83	60.29
SD	11.13	15.16	13.40
Median	57.50	59.95	59.40
Min, max	37.9, 75.1	38.6, 100.8	37.9, 100.8
Height, cm			
n	33	32	65
Mean	159.19	159.97	159.57
SD	9.00	9.40	9.14
Median	157.90	157.95	157.90
Min, max	139.6, 187.2	139.0, 176.9	139.0, 187.2
BMI, kg/m^2 †			
n	33	32	65
Mean	22.81	24.33	23.55
SD	4.09	4.20	4.18
Median	22.49	23.69	23.08
Min, max	15.2, 33.1	16.5, 34.6	15.2, 34.6

BMI: body mass index.
†: BMI was calculated as weight/(height^2).
Source: Table 12.1.2.1.1

Table 3 ACR50-CRP Response at Week 12 (NRI) (FAS)

Treatment Group	N	Responder n (%)	Treatment Difference vs Placebo		
			Difference † %	90% CI ‡ %	P-value §
Placebo	33	6 (18.2)	-11.9	(-25.0, 1.2)	0.258
ASP5094	32	2 (6.3)			

ACR: American College of Rheumatology; CI: confidence interval; CRP: C-reactive protein; FAS: full analysis set; NRI: nonresponder imputation.
N: Total number of responders and nonresponders (percentages based on N).
Subjects with all baseline ACR components data missing were not included in percentages.
†: Difference in proportion of responders (ASP5094 minus placebo).
‡: CI was calculated based on normal approximation of binomial distribution (Wald type).
§: Fisher's exact test.
Source: Table 12.3.1.1

Table 4 Overview of TEAEs (SAF)

Category	Number (%) of Subjects	
	Placebo (N = 33)	ASP5094 (N = 33)
TEAE	13 (39.4)	20 (60.6)
Mild	9 (27.3)	13 (39.4)
Moderate	4 (12.1)	6 (18.2)
Severe	0	1 (3.0)
Drug-related TEAE	2 (6.1)	5 (15.2)
Serious TEAE	1 (3.0)	2 (6.1)
Drug-related serious TEAE	0	1 (3.0)
Death	0	0
TEAE leading to permanent discontinuation of study drug	0	2 (6.1)
Drug-related TEAE leading to permanent discontinuation of study drug	0	1 (3.0)
Serious TEAE leading to permanent discontinuation of study drug	0	0
Drug-related serious TEAE leading to permanent discontinuation of study drug	0	0

SAF: safety analysis set; TEAE: treatment-emergent adverse event.
Source: Table 12.6.1.1 and Table 12.6.1.4

Table 5 TEAEs (SAF)

MedDRA (v20.0) SOC Preferred Term †	Number (%) of Subjects	
	Placebo (N = 33)	ASP5094 (N = 33)
Overall	**13 (39.4)**	**20 (60.6)**
Cardiac disorders	**1 (3.0)**	**0**
Cardiac failure	1 (3.0)	0
Gastrointestinal disorders	**3 (9.1)**	**5 (15.2)**
Constipation	1 (3.0)	3 (9.1)
Stomatitis	1 (3.0)	1 (3.0)
Dental caries	1 (3.0)	0
Diarrhoea	0	1 (3.0)
Vomiting	0	1 (3.0)
General disorders and administration site conditions	**2 (6.1)**	**3 (9.1)**
Chest discomfort	2 (6.1)	1 (3.0)
Pyrexia	0	1 (3.0)
Nodule	0	1 (3.0)
Infections and infestations	**8 (24.2)**	**8 (24.2)**
Viral upper respiratory tract infection	3 (9.1)	4 (12.1)
Influenza	1 (3.0)	2 (6.1)
Cystitis	1 (3.0)	1 (3.0)
Pneumonia	1 (3.0)	1 (3.0)
Bronchitis	0	1 (3.0)
Carbuncle	0	1 (3.0)
Gastroenteritis	1 (3.0)	0
Herpes virus infection	0	1 (3.0)
Periodontitis	1 (3.0)	0
Tinea pedis	1 (3.0)	0
Vulvovaginal candidiasis	1 (3.0)	0
Injury, poisoning and procedural complications	**1 (3.0)**	**1 (3.0)**
Spinal compression fracture	1 (3.0)	0
Tendon rupture	0	1 (3.0)
Investigations	**0**	**1 (3.0)**
White blood cell count decreased	0	1 (3.0)
Metabolism and nutrition disorders	**1 (3.0)**	**1 (3.0)**
Hypoglycaemia	0	1 (3.0)
Hyperlipidaemia	1 (3.0)	0
Musculoskeletal and connective tissue disorders	**4 (12.1)**	**8 (24.2)**
Rheumatoid arthritis	4 (12.1)	6 (18.2)
Arthritis	1 (3.0)	0
Back pain	0	1 (3.0)
Pain in extremity	1 (3.0)	0
Musculoskeletal stiffness	0	1 (3.0)

Table continued on next page

MedDRA (v20.0) SOC Preferred Term †	Number (%) of Subjects Placebo (N = 33)	 ASP5094 (N = 33)
Nervous system disorders	**0**	**1 (3.0)**
Headache	0	1 (3.0)
Respiratory, thoracic and mediastinal disorders	**2 (6.1)**	**1 (3.0)**
Cough	1 (3.0)	1 (3.0)
Bronchiectasis	1 (3.0)	0
Skin and subcutaneous tissue disorders	**3 (9.1)**	**1 (3.0)**
Eczema	1 (3.0)	1 (3.0)
Dermatitis	1 (3.0)	0
Dermatitis allergic	1 (3.0)	0

TEAE is defined as an adverse event observed from starting administration of the test drug/comparative drug to the end of study (i.e., week 16 or withdrawal + 4 weeks).
MedDRA; Medical Dictionary for Regulatory Activities; SAF: safety analysis set; SOC: system organ class, TEAE: treatment-emergent adverse event.
†: Sorting order: ascending order by SOC code and descending by the number of subjects of total group by Preferred Term. In case of ties, ascending order by Preferred Term code is applied.
Source: Table 12.6.1.2.1

Table 6 Drug-related TEAEs (SAF)

MedDRA (v20.0) SOC Preferred Term †	Number (%) of Subjects Placebo (N = 33)	 ASP5094 (N = 33)
Overall	**2 (6.1)**	**5 (15.2)**
Gastrointestinal disorders	**0**	**1 (3.0)**
Diarrhoea	0	1 (3.0)
General disorders and administration site conditions	**1 (3.0)**	**0**
Chest discomfort	1 (3.0)	0
Infections and infestations	**1 (3.0)**	**4 (12.1)**
Bronchitis	0	1 (3.0)
Cystitis	0	1 (3.0)
Influenza	0	1 (3.0)
Periodontitis	1 (3.0)	0
Pneumonia	0	1 (3.0)
Viral upper respiratory tract infection	0	1 (3.0)

TEAE is defined as an adverse event observed from starting administration of the test drug/comparative drug to the end of study (i.e., week 16 or withdrawal + 4 weeks).
MedDRA; Medical Dictionary for Regulatory Activities; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.
†: Sorting order: ascending order by SOC code and descending by the number of subjects of total group by Preferred Term. In case of ties, ascending order by Preferred Term code is applied.
Source: Table 12.6.1.3

Table 7 Serious TEAEs (SAF)

MedDRA (v20.0) SOC Preferred Term †	Number (%) of Subjects	
	Placebo (N = 33)	ASP5094 (N = 33)
Overall	**1 (3.0)**	**2 (6.1)**
Infections and infestations	**0**	**1 (3.0)**
Bronchitis	0	1 (3.0)
Influenza	0	1 (3.0)
Injury, poisoning and procedural complications	**1 (3.0)**	**1 (3.0)**
Spinal compression fracture	1 (3.0)	0
Tendon rupture	0	1 (3.0)

TEAE is defined as an adverse event observed from starting administration of the test drug/comparative drug to the end of study (i.e., week 16 or withdrawal + 4 weeks).
MedDRA; Medical Dictionary for Regulatory Activities; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.
†: Sorting order: Ascending order by SOC code and descending by the number of subjects of total group by Preferred Term. In case of ties, ascending order by Preferred Term code is applied.
Source: Table 12.6.1.6

Table 8 TEAEs Leading to Permanent Discontinuation of Study Drug (SAF)

MedDRA (v20.0) SOC Preferred Term †	Number (%) of Subjects	
	Placebo (N = 33)	ASP5094 (N = 33)
Overall	**0**	**2 (6.1)**
Infections and infestations	**0**	**1 (3.0)**
Pneumonia	0	1 (3.0)
Musculoskeletal and connective tissue disorders	**0**	**1 (3.0)**
Rheumatoid arthritis	0	1 (3.0)

TEAE is defined as an adverse event observed from starting administration of the test drug/comparative drug to the end of study (i.e., week 16 or withdrawal + 4 weeks).
MedDRA; Medical Dictionary for Regulatory Activities; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.
†: Sorting order: ascending order by SOC code and descending by the number of subjects of total group by Preferred Term. In case of ties, ascending order by Preferred Term code is applied.
Source: Table 12.6.1.8