Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: ASP5094		

SYNOPSIS

Title of Study: A Phase 1, Randomized, Placebo-controlled, Dose Escalation Study to Assess the Safety, Tolerability, and Pharmacokinetics of ASP5094 Following Multiple Intravenous Doses in Subjects With Rheumatoid Arthritis on Methotrexate (5094-CL-0102)

Investigators/Coordinating Investigator: [redacted], MD

Study Center(s): 12 clinical sites (5 in Poland and 7 in the US) participated in this study.

Publication Based on the Study: None

Study Period:

Study Initiation Date (Date of First Enrollment): 23 Feb 2016

Study Completion Date (Date of Last Evaluation): 07 Sep 2017

Phase of Development: Phase 1

Objectives: The primary objective was to evaluate the safety, tolerability and pharmacokinetics of multiple ascending intravenous doses of ASP5094 in male and female patients with rheumatoid arthritis (RA) on methotrexate (MTX).

Methodology: This was a phase 1, randomized, investigator- and patient-blinded, placebo-controlled, multiple ascending dose study to assess safety, tolerability and pharmacokinetics in patients with RA on stable doses of MTX.

Three sequential cohorts (A, B and C) received increasing intravenous doses of ASP5094 (1, 3 or 10 mg/kg) or placebo every 4 weeks for 3 doses (days 1, 29 and 57). Each cohort consisted of 10 patients with a 4:1 randomization ratio of ASP5094 (n = 8) to placebo (n = 2). After all patients in a cohort had completed study procedures through approximately day 36 (i.e., 7 days after the second dose administration), the overall safety and tolerability of the dose was determined after evaluation of the safety data (adverse events [AEs], vital signs, 12-lead electrocardiograms [ECGs]) and clinical laboratory tests (hematology, biochemistry, urinalysis and blinded peripheral lymphocyte subsets) for the current cohort and cumulative AE data from previous cohorts. Available pharmacokinetic and/or pharmacodynamic data ([redacted]) could also have been reviewed by the sponsor, as applicable.

If there were no events that met the stopping criteria, the next sequential cohort began enrollment while the current patients continued through the third dose and the remainder of the study.

Patients were screened up to 28 days prior to enrollment into 1 of 3 sequential cohorts. Randomization to ASP5094 or placebo occurred on day 1 within each cohort. Each cohort had the option to dose on the same day or in a staggered fashion based on patient enrollment dates at each investigative site.

Patients remained at the clinic until all postdose assessments on day 1 were completed. All patients repeated these procedures on each of the 2 remaining dosing days for a total of 3 doses. All patients had scheduled outpatient clinic visits and were followed for at least 12 weeks after the third and/or final study drug dose for safety, tolerability, pharmacokinetics, pharmacodynamics and antidrug antibodies. Samples for pharmacokinetics, pharmacodynamics and antidrug antibody assessments were collected for patients at prespecified time points.

Number of Patients (Planned, Enrolled and Analyzed): It was planned to enroll 30 patients (3 cohorts of 10 patients each [8 ASP5094, 2 placebo]). A total of 30 patients (24 ASP5094, 6 placebo) were randomized into the study. All patients were included in the safety analysis set (SAF) and pharmacodynamic analysis set (PDAS). All patients from the SAF, except those who received placebo, were included in the pharmacokinetic analysis set (PKAS).

Diagnosis and Main Criteria for Inclusion: The study population consisted of adult patients with RA on a stable dose of MTX. Key exclusion criteria included ongoing clinically significant systemic disease such as uncompensated heart failure, uncontrolled diabetes mellitus, severe hepatic failure, severe pulmonary disease or inflammatory bowel disease; a history of any malignancy in the past 5 years, except for adequately-treated, nonmelanoma skin cancer and adequately-treated in-situ cervical cancer; and a history of severe allergic or anaphylactic reactions to drugs. Patients must have been on concomitant MTX for ≥ 3 months and at a stable dose (10-25 mg/week) for ≥ 28 days prior to study drug dosing on day 1 and throughout the study. Use of folic acid was allowed. Patients must have been on a stable dose for ≥ 28 days prior to screening and continue on that dose throughout the study. Patients could continue to take stable background therapy for nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, acetaminophen (up to 2 g/day), hydroxychloroquine (Plaquenil), sulfasalazine (e.g., Azulfidine), oral corticosteroids (≤ 10 mg of prednisone, or equivalent, daily) or low-dose opioids (≤ 30 mg of oral morphine, or equivalent, daily) which had to have been taken at a stable dose for ≥ 28 days prior to screening. The start of Plaquenil and sulfasalazine (e.g., Azulfidine) must have been ≥ 2 months prior to study drug dosing on day 1. Patients must also have remained on stable doses of concomitant medications used to treat other preexisting conditions throughout the study. Patients should not have received any live or live-attenuated vaccine until 90 days after the third and/or final study drug dose. Any premedication prior to drug infusion was not allowed.

Test Product, Dose and Mode of Administration, Batch Numbers: ASP5094 solution for injection 40 mg/4 mL was administered intravenously over 30 minutes via syringe or programmable infusion pump at dose levels of 1, 3 or 10 mg/kg.

The batch number used in this study was 15132.

Duration of Treatment (or Duration of Study, if applicable): Patients received ASP5094 or placebo every 4 weeks (on days 1, 29 and 57) for a total of 3 doses.

Reference Product, Dose and Mode of Administration, Batch Numbers: Placebo (normal saline [0.9% sodium chloride injection]) was administered intravenously over 30 minutes via syringe or programmable infusion pump. The saline was supplied by the study sites from commercial sources.

Criteria for Evaluation:

Pharmacokinetics

The following endpoints were assessed:

Primary endpoints:

- AUC_{tau}
- t_{max}
- C_{max}
- C_{trough}
- $R_{ac}(AUC)$
- $R_{ac}(C_{max})$

Secondary endpoints:

- $t_{1/2}$
- V_z
- CL
- Fluctuation

Pharmacodynamics

The following parameters were assessed:

Exploratory endpoints:

[redacted]

Safety

The following parameters were assessed:

Primary endpoints:

- AEs
- Clinical laboratory tests (hematology, biochemistry and urinalysis)
- Vital signs (supine blood pressure, pulse, body temperature)
- Physical examination abnormalities
- 12-lead ECG measurements
- Total lymphocyte counts and peripheral lymphocyte subsets
- Anti-ASP5094 antibody formation

Statistical Methods:

Pharmacokinetics: The PKAS consisted of all SAF patients for whom serum concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter and for whom the time of dosing on day of sampling was known. Descriptive statistics (number of patients, mean, SD, % coefficient of variation [CV], median, minimum, maximum and, where applicable, geometric mean and geometric %CV) were used to

summarize, by dose level, the serum ASP5094 concentrations at each scheduled time as well as the pharmacokinetic parameters. Individual and mean serum ASP5094 concentration-time profiles on linear and semilogarithmic scales were provided. Overlay plots by treatment were also provided.

Dose proportionality was assessed for serum pharmacokinetic parameters AUC_{tau} and C_{max} across the 3 ASP5094 groups using the following power model:

$$\ln(Y_i) = \beta_0 + \beta_1 \cdot \ln(D) + \varepsilon_i$$

where Y_i was the pharmacokinetic parameter for patient i, D was the dose, ε_i was the random error and β_0 and β_1 were the intercept and slope, respectively.

Dose proportionality was declared if the 90% confidence interval for β_1 lay entirely within the critical region:

$$\left(1 + \frac{\ln(0.5)}{\ln(r)}, 1 + \frac{\ln(2)}{\ln(r)}\right)$$

where r was the ratio of the highest and the lowest dose in the study.

A graphical display of dose proportionality were provided for the pharmacokinetic parameters (AUC_{tau} and C_{max}) using standard figures.

Natural log transformed scatter plots (ln-ln), including the regression line, of C_{max} and AUC_{tau} versus dose were also provided.

Degree of accumulation for ASP5094 was assessed using the ratio of C_{max} ($R_{ac}[C_{max}]$) and AUC_{tau} ($R_{ac}[AUC_{tau}]$) after the first dose and the third dose.

Attainment of steady-state was examined using visual inspection of box and whisker plots of trough concentrations (C_{trough}) against dosing day, for days 29, 57 and 85.

Individual subject profiles (spaghetti plot) of trough concentrations versus day overlaid with the mean profile were also provided.

ASP5094 did not reach steady state following 3 doses (1, 3 or 10 mg/kg) and appeared to show nonlinear pharmacokinetics (target-mediated drug disposition). Therefore, the following pharmacokinetic parameters were not reported: AUC_{tau}, $t_{1/2}$, CL, V_z and Fluctuation (%). For reporting purposes, AUC_{tau} was replaced by $AUC_{57\text{-}85}$ for dose 3 (on day 57). Consequently, other parameters based on AUC_{tau}, such as dose normalized AUC and the accumulation parameter R_{ac}(AUC), were derived using $AUC_{0\text{-}28}$ and $AUC_{57\text{-}85}$. R_{ac}(AUC) and $R_{ac}(C_{max})$ were renamed as $R3_{ac}$(AUC) and $R3_{ac}(C_{max})$. Statistical assessment of dose proportionality was based on $AUC_{57\text{-}85}$ values instead of day 57 AUC_{tau}.

Pharmacodynamics: [redacted]

[redacted]

Safety: The SAF consisted of all randomized patients who took at least 1 dose of study drug.

For all safety data, summaries were provided for each ASP5094 dose level and placebo pooled across cohorts.

All safety and tolerability data for the SAF were listed. Results from unscheduled tests and screening assessments will be listed only (unless it contributes as a baseline value). No formal statistical testing were performed on these data.

AEs were coded using MedDRA version 17.0. The number and percentage of patients with treatment-emergent adverse events (TEAEs), drug-related TEAEs, serious TEAEs, drug-related serious TEAEs, TEAEs leading to withdrawal of treatment, drug-related TEAEs leading to withdrawal of treatment, TEAEs excluding serious adverse events ≥ 5% in any treatment group, TEAEs leading to death and drug-related TEAEs leading to death were summarized by SOC, preferred term and treatment.

For quantitative laboratory measurements, descriptive statistics were used to summarize results and change from baseline by treatment and visit.

Each out of range laboratory result was classified as low or high according to the laboratory supplied reference ranges.

Laboratory abnormalities that were considered potentially clinically significant by the investigator were recorded in the database as AEs.

Descriptive statistics were used to summarize vital signs results and changes from baseline by treatment and visit.

Tables for potentially clinically significant vital signs were generated using baseline value and highest/lowest value obtained during treatment for each patient for each treatment group.

The overall interpretation of routine 12-lead safety ECG results (normal, abnormal not clinically significant and abnormal clinically significant) was summarized by treatment and visit. The ECG results were also displayed by patient in a listing.

Descriptive statistics were to be used to summarize the anti-ASP5094 antibody data for each ASP5094 dose level and pooled placebo separately. A listing was provided for the anti-ASP5094 antibody data.

Descriptive statistics were used to summarize total lymphocyte counts and peripheral lymphocyte subsets for each ASP5094 dose level and placebo pooled across cohorts.

Summary of Results/Conclusions:

Population: A total of 30 patients were randomized into the study, 28 patients (5 placebo, 23 ASP5094) completed treatment and 2 patients (1 placebo, 1 ASP5094) permanently discontinued study drug due to a TEAE after receiving 2 of 3 planned doses Table 1. A total of 27 patients (5 placebo, 22 ASP5094) completed the study and 3 patients (1 placebo, 2 ASP5094) discontinued from the study for reasons listed in Table 1

All patients were included in the SAF and PDAS. All patients from the SAF, except those who received placebo, were included in the PKAS Table 1.

Female patients comprised half of the placebo group and the majority of all ASP5094 groups Table 2. The majority of patients were White and not Hispanic or Latino. The median age was 57.0 years in the placebo group and ranged from 54.5 to 60 years across the ASP5094 groups.

Pharmacokinetic Results:

- The pharmacokinetic disposition of ASP5094 was nonlinear over the ASP5094 dose range of 1 to 10 mg/kg.
- ASP5094 was administered intravenously over a 30-minute window. C_{max} was achieved at end of infusion.
- Both $R3_{ac}(C_{max})$ and $R3_{ac}(AUC)$ appeared to increase with increasing dose from 1 to 10 mg/kg.
- Dose proportionality for $AUC_{57\text{-}85}$ was not observed Table 3. C_{max} on day 57 was proportional to dose.

Pharmacodynamic Results:

[redacted]

Safety Results:

During the study, no deaths were reported, 1 serious adverse event was reported for 1 patient (10 mg/kg ASP5094) and 2 patients (placebo and 1 mg/kg ASP5094) each experienced 1 TEAE leading to permanent

discontinuation of study drug. No difference in nature and frequency of TEAEs or study drug-related TEAEs between treatments groups was noted and no dose-response relationship was observed.

The most common TEAEs (reported by more than 2 patients) included RA (exacerbation or flare) (2 patients 1 mg/kg ASP5094, 1 patient 3 mg/kg ASP5094) and nasopharyngitis (1 patient placebo, 2 patients 10 mg/kg ASP5094) [Table 4].

In general, the incidence of laboratory values above or below the normal laboratory ranges was low and there was no consistent pattern that would indicate an ASP5094-related effect. TEAEs were reported for 2 ASP5094-treated patients due to changes in clinical laboratory values (elevations in alanine aminotransferase and/or aspartate aminotransferase). Of these 2 patients, 1 patient was found to be positive for hepatitis E and the patient's TEAE was considered by the investigator as moderate in severity and not related to study drug. The TEAE of the other patient, which resolved within 9 days, was considered by the investigator to be mild in severity and possibly related to study drug.

No marked differences in prespecified changes in vital signs were observed between placebo and ASP5094 treatment groups. No evidence of dose-dependent changes in vital signs was observed across ASP5094 treatment groups.

A clinically significant ECG abnormality was observed in 1 patient (placebo) and was reported as a TEAE that was considered by the investigator to be mild in severity and related to study drug. This TEAE led to permanent discontinuation of study drug. None of the other observed ECG abnormalities or shifts from baseline findings were considered to be clinically significant.

The mean changes from baseline in lymphocyte counts and peripheral lymphocyte subsets suggested no dose-dependent changes after 3 intravenous doses of ASP5094 (on days 1, 29 and 57) compared to placebo.

None of the patients had confirmed positive titers for anti-ASP5094 antibodies.

CONCLUSIONS:

ASP5094, a first-in-class recombinant humanized immunoglobulin G1 monoclonal antibody targeting human alpha9 integrin, has been evaluated in this phase 1, randomized, investigator- and patient-blinded, placebo-controlled study designed to assess safety, tolerability and pharmacokinetics of multiple ascending intravenous doses of ASP5094 in patients with RA on stable doses of MTX. Patients received intravenous doses of ASP5094 at 1, 3 or 10 mg/kg every 4 weeks on days 1, 29 and 57.

After 3 doses, steady-state concentrations of ASP5094 were not achieved; therefore, the pharmacokinetic parameters of AUC_{tau}, CL, V_z and Fluctuation (%) were not reported. $R3_{ac}(AUC)$ and $R3_{ac}(C_{max})$ were reported to demonstrate accumulations after 3 doses. Target-mediated drug disposition was observed in the pharmacokinetics of ASP5094, hence $t_{1/2}$ was not reported. The pharmacokinetic disposition of ASP5094 was nonlinear over the dose range of 1 to 10 mg/kg.

[redacted]

[redacted]

Overall, in this study multiple intravenous doses of ASP5094 from 1 to 10 mg/kg were safe and well tolerated and had an acceptable safety profile in patients with RA on stable doses of MTX.

Date of Report: 12 Feb 2018

Table 1 Patient Disposition and Analysis Sets (All Randomized Patients)

	Placebo	ASP5094			
	(n = 6) n (%)	1 mg/kg (n = 8) n (%)	3 mg/kg (n = 8) n (%)	10 mg/kg (n = 8) n (%)	Total (n = 24) n (%)
Randomized	6 (100)	8 (100)	8 (100)	8 (100)	24 (100)
Safety analysis set†	6 (100)	8 (100)	8 (100)	8 (100)	24 (100)
Pharmacokinetic analysis set‡	0	8 (100)	8 (100)	8 (100)	24 (100)
Pharmacodynamic analysis set§	6 (100)	8 (100)	8 (100)	8 (100)	24 (100)
Completed treatment					
Yes	5 (83.3)	7 (87.5)	8 (100)	8 (100)	23 (95.8)
No	1 (16.7)	1 (12.5)	0	0	1 (4.2)
Primary reason for treatment discontinuation					
Adverse event	1 (16.7)	1 (12.5)	0	0	1 (4.2)
Completed study¶					
Yes	5 (83.3)	8 (100)	7 (87.5)	7 (87.5)	22 (91.7)
No	1 (16.7)	0	1 (12.5)	1 (12.5)	2 (8.3)
Primary reason for study discontinuation					
Adverse event	0	0	1 (12.5)	0	1 (4.2)
Other	1 (16.7)	0	0	1 (12.5)	1 (4.2)

† All randomized patients who took at least 1 dose of study drug.

‡ All patients from the safety analysis set for whom serum concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter and for whom the time of dosing on day of sampling was known.

§ All patients from the safety analysis set for whom sufficient pharmacodynamic measurements were collected.

¶ Completed the day 113 and 141 visits.

Source: End-of-Text Tables 12.1.1.1, 12.1.1.2, 12.1.1.3 and 12.1.1.4

Table 2 Summary of Demographics and Baseline Characteristics (All Randomized Patients)

Parameter Category/ Statistics	Placebo (n = 6)	ASP5094 1 mg/kg (n = 8)	ASP5094 3 mg/kg (n = 8)	ASP5094 10 mg/kg (n = 8)	ASP5094 Total (n = 24)
Sex, n (%)					
Male	3 (50.0)	1 (12.5)	0	1 (12.5)	2 (8.3)
Female	3 (50.0)	7 (87.5)	8 (100)	7 (87.5)	22 (91.7)
Ethnicity, n (%)					
Hispanic or Latino	1 (16.7)	3 (37.5)	1 (12.5)	0	4 (16.7)
Not Hispanic or Latino	5 (83.3)	5 (62.5)	7 (87.5)	8 (100)	20 (83.3)
Race, n (%)					
White	6 (100)	4 (50.0)	8 (100)	8 (100)	20 (83.3)
Black or African American	0	4 (50.0)	0	0	4 (16.7)
Age (years)					
Mean (SD)	52.2 (11.8)	55.9 (4.9)	57.9 (6.2)	51.6 (9.7)	55.1 (7.4)
Median	57.0	56.0	60.0	54.5	56.0
Min – Max	31 – 63	48 – 62	46 – 64	33 – 64	33 – 64
Weight (kg)					
Mean (SD)	80.5 (20.9)	79.2 (15.3)	75.4 (5.9)	71.8 (10.9)	75.5 (11.3)
Median	82.1	79.3	76.2	74.3	77.5
Min – Max	53 – 113	51 – 101	67 – 84	58 – 85	51 – 101
Height (cm)					
Mean (SD)	163.9 (9.9)	162.3 (7.7)	161.2 (3.9)	165.2 (7.4)	162.9 (6.5)
Median	160.0	160.0	161.8	167.0	162.4
Min – Max	152 – 180	149 – 172	155 – 165	152 – 178	149 – 178
BMI (kg/m^2)					
Mean (SD)	29.6 (5.4)	29.8 (4.0)	29.0 (2.0)	26.2 (3.0)	28.3 (3.3)
Median	30.2	30.3	29.5	26.2	28.6
Min – Max	23 – 35	23 – 35	26 – 32	22 – 30	22 – 35

BMI: body mass index (weight [kg]/height^2 [m^2]); Max: maximum; Min: minimum.

Source: End-of-Text Table 12.1.2.1

Table 3 Statistical Assessment of Dose Proportionality for ASP5094 for All Cohorts, Power Model (PKAS)

Dose Range	Parameter	Slope Estimate (SE)	90% CI of Slope	Prespecified Limits†
1 – 10 mg/kg	$AUC_{57\text{-}85}$ (day•µg/mL)	1.56 (0.0606)	(1.45, 1.66)	(0.699, 1.30)
	C_{max} (µg/mL)	1.13 (0.0437)	(1.06, 1.21)	(0.699, 1.30)

All patients from the SAF for whom concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter and for whom the time of dosing on day of sampling was known (PKAS).

Assessment based on the power model (linear regression of natural-log transformed parameter and dose).

CI: confidence interval; PKAS: pharmacokinetic analysis set; SAF: safety analysis set; SE: standard error.

† Dose proportionality concluded in specified dose range if 90% CI of slope is entirely within the prespecified limits.

Source: End-of-Text Table 12.4.3

Table 4 Summary of TEAEs by Dose Group (SAF)

MedDRA v17.0 SOC Preferred Term	Placebo (n = 6) n (%)	ASP5094 1 mg/kg (n = 8) n (%)	ASP5094 3 mg/kg (n = 8) n (%)	ASP5094 10 mg/kg (n = 8) n (%)	ASP5094 Total (n = 24) n (%)
Overall	**4 (66.7)**	**6 (75.0)**	**6 (75.0)**	**6 (75.0)**	**18 (75.0)**
Cardiac Disorders	**1 (16.7)**	**0**	**1 (12.5)**	**0**	**1 (4.2)**
Tachycardia	0	0	1 (12.5)	0	1 (4.2)
Atrioventricular block second degree	1 (16.7)	0	0	0	0
Gastrointestinal Disorders	**1 (16.7)**	**0**	**0**	**1 (12.5)**	**1 (4.2)**
Diarrhoea	0	0	0	1 (12.5)	1 (4.2)
Nausea	0	0	0	1 (12.5)	1 (4.2)
Abdominal pain upper	1 (16.7)	0	0	0	0
General Disorders and Administration Site Conditions	**0**	**0**	**3 (37.5)**	**2 (25.0)**	**5 (20.8)**
Oedema peripheral	0	0	1 (12.5)	1 (12.5)	2 (8.3)
Chest discomfort	0	0	1 (12.5)	0	1 (4.2)
Infusion site extravasation	0	0	1 (12.5)	0	1 (4.2)
Noncardiac chest pain	0	0	1 (12.5)	0	1 (4.2)
Pyrexia	0	0	0	1 (12.5)	1 (4.2)
Infections and Infestations	**1 (16.7)**	**0**	**5 (62.5)**	**3 (37.5)**	**8 (33.3)**
Nasopharyngitis	1 (16.7)	0	0	2 (25.0)	2 (8.3)
Gastroenteritis viral	0	0	1 (12.5)	1 (12.5)	2 (8.3)
Laryngitis	0	0	0	1 (12.5)	1 (4.2)
Oral herpes	0	0	0	1 (12.5)	1 (4.2)
Rhinitis	0	0	0	1 (12.5)	1 (4.2)
Subcutaneous abscess	0	0	1 (12.5)	0	1 (4.2)
Tooth abscess	0	0	1 (12.5)	0	1 (4.2)
Upper respiratory tract infection	0	0	1 (12.5)	0	1 (4.2)
Urinary tract infection	0	0	1 (12.5)	0	1 (4.2)
Investigations	**0**	**1 (12.5)**	**1 (12.5)**	**1 (12.5)**	**3 (12.5)**
Alanine aminotransferase increased	0	0	0	1 (12.5)	1 (4.2)
Liver function test abnormal	0	1 (12.5)	0	0	1 (4.2)
Weight decreased	0	0	1 (12.5)	0	1 (4.2)
Metabolism and nutrition disorders	**0**	**0**	**1 (12.5)**	**0**	**1 (4.2)**
Hypercholesterolaemia	0	0	1 (12.5)	0	1 (4.2)
Musculoskeletal and Connective Tissue Disorders	**2 (33.3)**	**3 (37.5)**	**2 (25.0)**	**2 (25.0)**	**7 (29.2)**
Rheumatoid arthritis	0	2 (25.0)	1 (12.5)	0	3 (12.5)
Joint swelling	0	0	0	1 (12.5)	1 (4.2)
Musculoskeletal chest pain	0	0	1 (12.5)	0	1 (4.2)
Musculoskeletal pain	0	0	0	1 (12.5)	1 (4.2)
Osteoporosis	0	1 (12.5)	0	0	1 (4.2)
Arthritis	1 (16.7)	0	0	0	0
Synovitis	1 (16.7)	0	0	0	0
Nervous System Disorders	**0**	**2 (25.0)**	**0**	**1 (12.5)**	**3 (12.5)**
Headache	0	1 (12.5)	0	1 (12.5)	2 (8.3)
Tremor	0	1 (12.5)	0	0	1 (4.2)
Respiratory, Thoracic and Mediastinal Disorders	**0**	**0**	**0**	**1 (12.5)**	**1 (4.2)**
Dysphonia	0	0	0	1 (12.5)	1 (4.2)
Laryngeal oedema	0	0	0	1 (12.5)	1 (4.2)
Skin and Subcutaneous Tissue Disorders	**0**	**1 (12.5)**	**0**	**1 (12.5)**	**2 (8.3)**
Dermatis allergic	0	0	0	1 (12.5)	1 (4.2)
Rash	0	1 (12.5)	0	0	1 (4.2)

All randomized patients who took at least 1 dose of study drug (SAF).

Footnotes continued on next page

TEAEs were sorted by alphabetical order of the SOCs and within the SOCs by descending incidence of preferred terms in the ASP5094 total group and, in case of ties, alphabetically.

A TEAE was defined as a newly occurring or worsening AE observed after starting administration of study drug up until the end of study visit, inclusive.

AE: adverse event; SAF: safety analysis set; TEAE: treatment-emergent adverse event.

Source: End-of-Text Table 12.6.1.2