Name of Sponsor/Company: Astellas Pharma Inc.		
Name of Finished Product: Not Applicable		
Name of Active Ingredient: ASP1707		

SYNOPSIS

Title of Study: A randomized, placebo-controlled, double-blind, parallel group phase 2a study of ASP1707 in postmenopausal female patients with rheumatoid arthritis (RA) taking methotrexate (MTX)

Investigators/Coordinating Investigator: [redacted], [redacted]

Study Center(s): 27 contracted sites in Japan

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

Study Period:

Study Initiation Date (Date of First Informed Consent): 16 Sep 2016

Study Completion Date (Date of Last Evaluation): 25 Oct 2017

Phase of Development: Phase 2a

Objectives: To evaluate the efficacy of ASP1707 (30 mg bid) used in combination with MTX in postmenopausal female patients with RA; and to evaluate the pharmacokinetics, pharmacodynamics and safety.

Methodology: This study was a multi-center, randomized, placebo-controlled, double-blind, parallel group study to evaluate the efficacy and safety of ASP1707 (30 mg bid) used in combination with MTX in postmenopausal female patients who had moderate to severe active RA despite using MTX. Patients were randomized to ASP1707 or placebo in a 1:1 ratio at baseline after the screening period. The study drug was orally administered twice a day for 12 weeks in the treatment period.

Number of Patients (Planned, Enrolled and Analyzed): The number of patients planned for the study was a total of 70 patients (ASP1707 group: 35 patients, placebo group: 35 patients). A total of 72 patients were randomized (ASP1707: 37, placebo: 35) and 65 patients completed the study (ASP1707: 32, placebo: 33).

Diagnosis and Main Criteria for Inclusion: Patients who had provided written informed consent prior to any study-specific procedures, and being candidates for participation in the study were screened for the following inclusion/exclusion criteria before enrollment into the study. The patient's eligibility to participate in this study was confirmed based on the examination results obtained during screening period and at baseline.

Inclusion:

1. Institutional Review Board (IRB)-approved written informed consent must be obtained from the patient prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).

2. The patient was a natural postmenopausal female whose last regular menstrual cycle was at least 24 months ago at the time of informed consent.
3. The patient had a follicle stimulating hormone (FSH) level of ≥ 30 mIU/mL at screening, unless patient was ≥ 60 years of age.
4. The patient 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.
5. The patient met the 1991 ACR Revised Criteria for the Classification of Global Functional Status in RA Class I, II or III at screening.
6. At screening, the patient had active RA as evidenced by both of the following:
   - ≥ 6 tender/painful joints (using 68-joint assessment)
   - ≥ 6 swollen joints (using 66-joint assessment)
7. The patient had a C-reactive protein (CRP) level (latex agglutination method) of > 0.3 mg/dL or an erythrocyte sedimentation rate (ESR) of > 28 mm/h at screening.
8. The patient who had continuously received MTX for at least 90 days prior to screening and who was able to continue a stable dose of MTX from at least 28 days prior to screening through the screening and treatment periods until the end of the follow-up period.
9. The patient who had received none of the following drugs or had received any of the drugs with stable dosage for at least 28 days prior to baseline (this criterion did not apply to rescue medications; for details, refer to regulations regarding rescue medications):
   Non-steroidal anti-inflammatory drugs (NSAIDs; excluding topical formulations for external use), oral morphine (≤ 30 mg/day) or equivalent opioid analgesics, acetaminophen and oral corticosteroids (≤ 5 mg/day in prednisolone equivalent)
10. The patient agreed not to participate in another interventional study during the present study.

Exclusion:

1. The patient had deviated from the criteria for prohibited medications/therapies, limited medications or rescue medications before baseline.
2. The patient became amenorrhoeic by surgery.
3. The patient was determined to be an inadequate responder to a prior biologic disease-modifying antirheumatic drug (DMARD) by the investigator/subinvestigator (excluding patients who were not able to continue a biologic DMARD from the perspective of tolerability).
4. The patient had a contraindication or hypersensitivity to gonadotropin releasing hormone (GnRH) analogs.
5. The patient had participated in a clinical trial or postmarketing clinical study of another ethical drug or medical device within 12 weeks (84 days) or within 5 half-lives, whichever was longer, prior to screening.
6. The patient had undergone invasive surgical therapy which, in the opinion of the investigator/subinvestigator, still affected the joints to be assessed, or was scheduled to undergo surgical therapy which, in the opinion of the investigator/subinvestigator, might affect the joints to be assessed during the treatment or follow-up period.
7. The patient had another inflammatory arthritis than RA (e.g., psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, sarcoidosis, gouty arthritis).
8. The patient met any of the following criteria for laboratory values at screening:
   - White blood cell count < 4000/μL

- Platelet count < 100000/μL
- Alanine Aminotransferase (ALT) ≥ 2 × upper limit of normal (ULN)
- Aspartate Aminotransferase (AST) ≥ 2 × ULN
- Total bilirubin (TBL) ≥ 1.5 × ULN
- Hepatitis B surface antigen-, hepatitis B virus-DNA quantitation- or hepatitis C virus antibody-positive

9. The patient 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 including other test methods might be allowed. If a retest was not performed, the criteria for positive results would be followed.)
10. The patient had a history of or concurrent pituitary adenoma.
11. The patient had a high risk of fractures (had a history of or concurrent non-traumatic fractures in vertebral body/femur, etc.).
12. The patient had been diagnosed with osteoporosis, which was still left untreated.
13. The patient had a history of or concurrent malignant tumor.
14. The patient had any severe, progressive or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiac, neurological, infectious or autoimmune disease except for RA (excluding Sjogren's syndrome and chronic thyroiditis).
15. The patient 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 requiring hospitalization).
16. The patient had clinically significant abnormalities on 12-lead electrocardiogram (ECG) at screening.
17. The patient had a history of human immunodeficiency virus infection.
18. Any condition which, in the opinion of the investigator/subinvestigator, made the patient unsuitable for study participation.

Test Product, Dose and Mode of Administration, Lot Numbers: ASP1707 10 mg tablets, oral, 30 mg twice daily, [redacted]

Duration of Treatment (or Duration of Study, if applicable): Three ASP1707 10 mg tablets each was administered twice a day for 12 weeks in combination with MTX therapy.

Reference Product, Dose and Mode of Administration, Lot Numbers: Since this study was a multi-center, randomized, placebo-controlled, double-blind, parallel group study to evaluate the efficacy and safety of ASP1707 (30 mg bid) used in combination with MTX, the ASP1707 placebo tablet which was indistinguishable from ASP1707 10 mg tablet in appearance was used as comparative drug.

ASP1707 placebo tablets, oral, 3 tablets twice daily, [redacted]

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

Primary efficacy endpoint:

- ACR20 response rate at Week 12

Secondary efficacy endpoints:

- ACR20 response rate at Weeks 1, 2, 4 and 8

The following secondary endpoints at Weeks 1, 2, 4, 8 and 12:

- ACR50 response rate
- ACR70 response rate
- Change from baseline in the disease activity score (DAS) 28-CRP or DAS28-ESR score
- Change from baseline in Tender Joint Count (TJC) (68 joints)
- Change from baseline in Swollen Joint Count (SJC) (66 joints)
- Percentage of patients who have achieved a DAS28-CRP or DAS28-ESR score for remission (< 2.6)
- Percentage of patients who have achieved a DAS28-CRP or DAS28-ESR score for low disease activity (≤ 3.2)
- Change from baseline in CRP and ESR
- Percentage of patients who have achieved a good response according to the EULAR response criteria
- Percentage of patients who have achieved a good or moderate response according to the EULAR response criteria
- Percentage of patients who have achieved an ACR/EULAR score for remission. ACR/EULAR remission is defined as meeting all of the following four criteria:
  - TJC ≤ 1
  - SJC ≤ 1
  - CRP ≤ 1.0 mg/dL
  - Subject's global assessment of arthritis (SGA) ≤ 10 mm (100-mm visual analog scale [VAS])
- Percentage of patients who have achieved a simplified disease activity index (SDAI) score ≤ 3.3 (SDAI remission)
- Change from baseline in the SDAI score
- Change from baseline in the health assessment questionnaire - disability index (HAQ-DI)

Pharmacokinetic variables: plasma concentrations of ASP1707 and its metabolite (AS1948006)

Pharmacodynamic variables: endocrinology (serum estradiol [E2], FSH, luteinizing hormone [LH] and progesterone), tumor necrosis factor α (TNF-α), matrix metalloproteinase 3 (MMP3) and interleukin (IL)-6

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

Statistical Methods:

Efficacy:

For the analysis of primary endpoint, the ACR20-CRP response rates at Week 12 were compared between the two treatment groups based on the full analysis set (FAS). For testing the statistical significance of ASP1707 effect, chi-square test (no continuity correction) was used accompanying the associated two-sided P-values. The difference of the ACR20-CRP response rate between the two treatment groups and its two-sided 90% confidence interval (based on normal approximation) were also calculated.
For the imputation of missing data on the ACR20-CRP response at Week 12, the non-responder imputation (NRI) method, which handled a patient withdrawn from the study prematurely before Week 12 or otherwise had missing data as a non-responder, was used.

Secondary endpoints were analyzed based on FAS as follows:

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

- Time to event variables were compared between the two treatment groups using the log-rank test and the hazard ratio was calculated using the Cox proportional hazard model.

Pharmacokinetics/Pharmacodynamics:

For pharmacokinetic and pharmacodynamic parameters, summary statistics were presented.

Safety:

Adverse events:

The number and percentage of patients with TEAEs and number of TEAEs, as classified by SOC and preferred term (PT) coded using the MedDRA/Japanese version (MedDRA/J) v19.0 were summarized for safety analysis set (SAF). Summaries were provided for:

The number and percentage of TEAEs,
The number and percentage of Serious TEAEs,
The number and percentage of TEAEs leading to permanent discontinuation of study drug,
The number and percentage of Drug related TEAEs,
The number and percentage of TEAEs by severity.

Laboratory parameters, vital signs, body weight and 12-lead ECG:

Raw values and changes from baseline at each scheduled visit were summarized using descriptive statistics or frequency tabulation.

Summary of Results/Conclusions:

Population:

In total, 105 patients provided written informed consent and 33 patients failed screening. A total of 72 patients were randomized. Of the 72 patients randomized, 65 patients completed the study and 7 patients discontinued the study [Figure 1].

Of 72 randomized patients, all 72 patients were included in the FAS. The PPS consisted of 66 patients. The SAF, pharmacokinetic analysis set (PKAS) and pharmacodynamic analysis set (PDAS) consisted of all 72 randomized patients [Table 1].

The mean (SD) ages of patients in the placebo and ASP1707 groups were 61.7 (7.5) and 64.3 (7.5) years, and the percentage of the patients equal or older than 65 years were 42.9 and 45.9%, respectively. The body mass indexes (BMI) were 23.25 (3.58) and 22.45 (4.14) kg/m^2, and the times since the last menstruation were 137.7 (81.7) and 170.7 (96.0) months, respectively.

The mean (SD) LH in the placebo and ASP1707 groups were 22.829 (9.177) and 22.312 (9.120) IU/L, and FSH were 55.375 (17.006) and 54.629 (18.533) IU/L, respectively [Table 2].

The mean (SD) TJC (68 joints) in the placebo and ASP1707 groups were 13.4 (7.5) and 14.7 (9.2), SJC (66 joints) being 10.8 (4.5) and 10.7 (4.7), the DAS28-CRP being 4.71 (0.93) and 4.77 (0.83), and the DAS28-ESR being 5.51 (0.94) and 5.52 (0.84), respectively. The CRP were 0.957 (0.877) and 1.256 (1.444) mg/dL, and ESR being 39.0 (18.0) and 38.0 (19.2) mm/h, respectively. No notable difference between placebo and ASP1707 groups was observed in any demographics and baseline characteristics parameters.

The mean (SD) durations of study drug exposure were 81.3 (11.6) and 76.0 (18.8) days in the placebo and ASP1707 groups, respectively. The patients experienced ≥ 90% of treatment compliance were 100.0% and 94.6% in the placebo and ASP1707 groups, respectively. There was no difference in treatment compliance between treatment groups.

Efficacy/Pharmacokinetic/Pharmacodynamic Results:

Efficacy:

For the primary efficacy endpoint, ACR20 response at Week 12 (NRI) in FAS, were 37.1% in placebo group and 32.4% in ASP1707 group, and the difference between the treatment groups (ASP1707 - Placebo) was -4.7%. There was no statistically significant difference between ASP1707 and placebo groups (P = 0.675) [Table 3].

For the major secondary efficacy endpoints, the percentage of patients achieving ACR20 response at Weeks 1, 2, 4, 8 provided no significant improvement in ASP1707 group in comparison with the placebo group throughout the treatment period. The ACR50 response rate, ACR70 response rate, DAS28-CRP scores, CRP, percentage of patients achieving DAS28-ESR score < 2.6 at Week 12 showed the similar results, no significant difference between ASP1707 and placebo groups.

Pharmacokinetics:

The mean plasma concentrations of ASP1707 and AS1948006 were 8.17 ng/mL and 50.0 ng/mL at Week 1, 12.5 ng/mL and 45.7 ng/mL at Week 2, 64.6 ng/mL and 170 ng/mL at Week 4, 7.24 ng/mL and 47.4 ng/mL at Week 8 and 6.48 ng/mL and 43.6 ng/mL at Week 12, respectively.

Pharmacodynamics:

Following the oral administration of ASP1707 30 mg twice a day, LH decreased rapidly to less than 1 IU/L at Week 1 and kept approximately 0.6 IU/L throughout the treatment period. FSH also decreased quickly to 4.683 (2.416) IU/L at Week 2 and kept approximately 3 IU/L from Week 4 throughout the treatment period. No apparent change of LH and FSH were observed in the placebo groups. However, the plasma levels of estradiol and progesterone did not decrease after oral administration of ASP1707 30 mg twice a day, as those in the placebo group. The other pharmacodynamic parameters (TNF-α, MMP3 and IL-6) did not decrease in both treatment groups.

Safety Results:

Adverse events:

The incidence of TEAEs was 54.3% (19/35) in the placebo group and 62.2% (23/37) in the ASP1707 group. The incidence of drug-related TEAEs was 14.3% (5/35) in the placebo group and 24.3% (9/37) in the ASP1707 group. All TEAEs were mild or moderate in severity, except for 1 severe event (cholelithiasis) reported in the placebo group. No deaths were reported during the study. One SAE (cholelithiasis) was observed in 1 patient in placebo group, which was not related to the study drug. The incidence of TEAEs leading to permanent discontinuation was 2.9% (1/35) in the placebo group and 5.4% (2/37) in the ASP1707 group [Table 4].

The common TEAEs (≥ 10% in any treatment group) by PT were nasopharyngitis and rheumatoid arthritis. The higher incidence of nasopharyngitis was observed in the ASP1707 group than that in the placebo group.

The drug-related TEAE that occurred more than 1 patient in PT was nasopharyngitis (8.1% [3/37]) in the ASP1707 group [Table 5].

No deaths were reported during the study. A serious TEAE was reported in 1 patient (2.9%) in the placebo group. The serious TEAE reported was cholelithiasis (reported term: gallbladder stone aggravated), the event being graded as severe in severity and not related in causality. The patient was also assessed as the potential drug-induced liver injury (DILI) case according to the laboratory test results.

A TEAE leading to permanent discontinuation reported in the placebo group was rheumatoid arthritis (reported term: rheumatoid arthritis aggravated). The event was mild in severity and considered as not related to the study drug. TEAEs leading to permanent discontinuation reported in the ASP1707 group were rheumatoid arthritis (reported term: rheumatoid arthritis aggravated) in 2 patients. Both events were reported as moderate and not related to the study drug.

Laboratory parameters, vital signs, body weight and 12-lead ECG:

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

CONCLUSIONS:

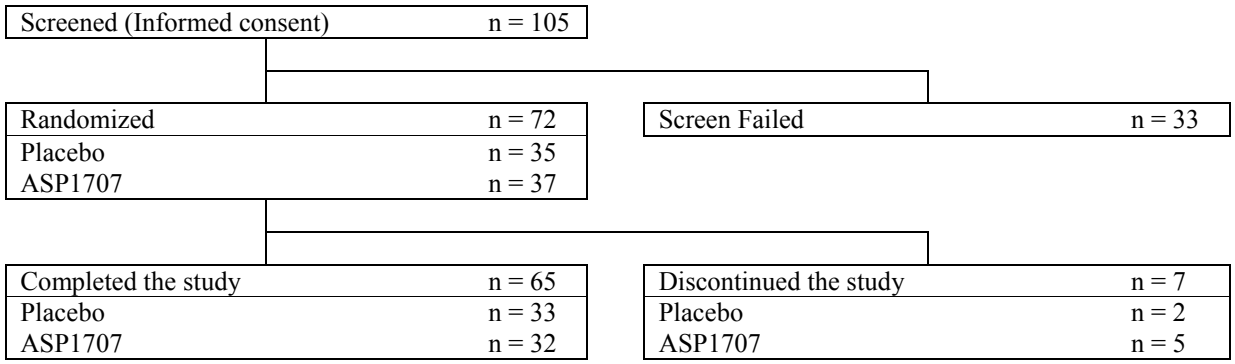
ASP1707 in combination with methotrexate was not efficacious in the treatment of moderate to severe rheumatoid arthritis in postmenopausal female patients.

ASP1707 in combination with methotrexate was safe and well tolerated.

Date of Report: 15 May 2018

Figure 1 Disposition of Patients

CONSORT Flow Diagrams



Source: Table 12.1.1.1, Table 12.1.1.2 and Table 12.1.1.3

Table 1 Analysis Sets

Population	Placebo (N = 35)	ASP1707 (N = 37)	Total (N = 72)
	n (%)	n (%)	n (%)
Randomized	35 (100.0%)	37 (100.0%)	72 (100.0%)
Full Analysis Set	35 (100.0%)	37 (100.0%)	72 (100.0%)
Per Protocol Set	34 (97.1%)	32 (86.5%)	66 (91.7%)
Safety Analysis Set	35 (100.0%)	37 (100.0%)	72 (100.0%)
Pharmacokinetic Analysis Set	35 (100.0%)	37 (100.0%)	72 (100.0%)
Pharmacodynamic Analysis Set	35 (100.0%)	37 (100.0%)	72 (100.0%)

Source: Table 12.1.1.2

Table 2 Demographics and Baseline Characteristics (FAS)

Parameter	Category/ Statistic	Placebo (N = 35)	ASP1707 (N = 37)	Total (N = 72)
Sex	Female	35 (100.0%)	37 (100.0%)	72 (100.0%)
Age (years)	Mean (SD)	61.7 (7.5)	64.3 (7.5)	63.0 (7.6)
	Min, Max	48, 75	52, 81	48, 81
Age Group, n (%)	< 65 Years	20 (57.1%)	20 (54.1%)	40 (55.6%)
	≥ 65 Years	15 (42.9%)	17 (45.9%)	32 (44.4%)
Weight (kg) at Baseline	Mean (SD)	54.05 (9.67)	53.35 (10.56)	53.69 (10.07)
	Min, Max	37.0, 76.1	35.4, 80.2	35.4, 80.2
Height (cm) at Baseline	Mean (SD)	152.29 (5.41)	154.06 (5.68)	153.20 (5.58)
	Min, Max	138.4, 160.4	141.7, 167.5	138.4, 167.5
BMI (kg/m^2) at Baseline	Mean (SD)	23.25 (3.58)	22.45 (4.14)	22.84 (3.87)
	Min, Max	16.7, 30.3	16.2, 32.8	16.2, 32.8
Time Since the Last Menstruation (months)	Mean (SD)	137.7 (81.7)	170.7 (96.0)	154.6 (90.2)
	Min, Max	24, 300	24, 396	24, 396
LH (IU/L)	Mean (SD)	22.829 (9.177)	22.312 (9.120)	22.564 (9.087)
	Min, Max	7.40, 47.65	6.16, 42.05	6.16, 47.65
LH Group, n (%)	≤ Median	15 (42.9%)	21 (56.8%)	36 (50.0%)
	> Median	20 (57.1%)	16 (43.2%)	36 (50.0%)
FSH (IU/L)	Mean (SD)	55.375 (17.006)	54.629 (18.533)	54.992 (17.686)
	Min, Max	23.89, 98.54	19.69, 102.51	19.69, 102.51
FSH Group, n (%)	≤ Median	17 (48.6%)	19 (51.4%)	36 (50.0%)
	> Median	18 (51.4%)	18 (48.6%)	36 (50.0%)

BMI: body mass index (BMI = weight [kg]/height^2 [m].); FSH: follicle stimulating hormone; LH: luteinizing hormone

Source: Table 12.1.2.1.2

Table 3 ACR20-CRP Response at Week 12 (NRI) (FAS)

			Treatment Difference vs Placebo		
Treatment Group	**N**	**Responder n (%)**	**Difference † %**	**90% CI ‡ %**	**P-value §**
Placebo	35	13 (37.1%)	-	-	-
ASP1707	37	12 (32.4%)	-4.7	(-23.2, 13.7)	0.675

CI: Confidence interval;
NRI: Non-responder imputation
N: Total number of responders and non-responders (percentages based on N)
Patients with all baseline ACR components data missing were not included in percentages.
†: Difference in proportion of responders (ASP1707 group minus placebo)
‡: CI was calculated based on normal approximation of binomial distribution (Wald type).
§: Chi-square test (no continuity correction)
Source: 12.3.1.1.1

Table 4 Overview of TEAEs (SAF)

	Placebo (N = 35)	**ASP1707 (N = 37)**	**Total (N = 72)**
	n (%)	**n (%)**	**n (%)**
TEAE	19 (54.3%)	23 (62.2%)	42 (58.3%)
Mild	15 (42.9%)	19 (51.4%)	34 (47.2%)
Moderate	3 (8.6%)	4 (10.8%)	7 (9.7%)
Severe	1 (2.9%)	0	1 (1.4%)
Drug-Related† TEAE	5 (14.3%)	9 (24.3%)	14 (19.4%)
Deaths	0	0	0
Serious TEAE	1 (2.9%)	0	1 (1.4%)
Drug-Related† Serious TEAE	0	0	0
TEAE Leading to Permanent Discontinuation of Study Drug	1 (2.9%)	2 (5.4%)	3 (4.2%)
Drug-Related† TEAE Leading to Permanent Discontinuation of Study Drug	0	0	0
Serious TEAE Leading to Permanent Discontinuation of Study Drug	0	0	0
Drug-Related† Serious TEAE Leading to Permanent Discontinuation of Study Drug	0	0	0

TEAE: Treatment-emergent adverse events are defined as any adverse event that started or worsened in severity after initial dose of study drug through the follow-up period.

†: Possible or probable, as assessed by the investigator.

Source: Table 12.6.1.1 and Table 12.6.1.4

Table 5 Drug-Related TEAEs (SAF)

MedDRA v19.0 System Organ Class Preferred Term	Placebo (N = 35) n (%)	ASP1707 (N = 37) n (%)	Total (N = 72) n (%)
Overall	5 (14.3%)	9 (24.3%)	14 (19.4%)
Gastrointestinal Disorders	1 (2.9%)	1 (2.7%)	2 (2.8%)
Constipation	0	1 (2.7%)	1 (1.4%)
Diarrhoea	1 (2.9%)	0	1 (1.4%)
Infections and Infestations	1 (2.9%)	5 (13.5%)	6 (8.3%)
Nasopharyngitis	0	3 (8.1%)	3 (4.2%)
Bronchitis	0	1 (2.7%)	1 (1.4%)
Influenza	1 (2.9%)	0	1 (1.4%)
Pulpitis dental	0	1 (2.7%)	1 (1.4%)
Investigations	2 (5.7%)	3 (8.1%)	5 (6.9%)
Lymphocyte count decreased	1 (2.9%)	1 (2.7%)	2 (2.8%)
Blood beta-D-glucan increased	1 (2.9%)	1 (2.7%)	2 (2.8%)
Neutrophil count decreased	0	1 (2.7%)	1 (1.4%)
Nervous system Disorders	1 (2.9%)	1 (2.7%)	2 (2.8%)
Dizziness	0	1 (2.7%)	1 (1.4%)
Headache	1 (2.9%)	0	1 (1.4%)

Source: Table 12.6.1.3