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# Full Novartis Clinical Trial Results Template

**Sponsor**

Novartis

**Generic Drug Name**

lanalumab

**Trial Indication(s)**

Rheumatoid arthritis (RA)

**Protocol Number**

CVAY736X2101

**Protocol Title**

A dose escalation study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of VAY736 in rheumatoid arthritis patients

**Clinical Trial Phase**

Phase I

**Phase of Drug Development**

Phase II

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**Study Start/End Dates**

20 Dec 2010 to 22 Jan 2018

**Reason for Termination (If applicable)**

N/A

**Study Design/Methodology**

This was a three-part study:

- Part 1 was double-blind, randomized and placebo-controlled which evaluated ascending single i.v. dose of VAY736 in RA patients,
- Part 2 was open-labeled which evaluated ascending single s.c. dose of VAY736 at two dose levels in RA patients, and
- Part 3 was open-labeled which evaluated multiple fixed s.c. doses of VAY736 in RA patients.

**Centers**

1 center in Germany

**Objectives:**

**Primary objective(s)**

Part 1

- To evaluate the safety of ascending single intravenous (i.v.) doses of VAY736 in rheumatoid arthritis (RA) patients

Part 2

- To evaluate the safety and tolerability of ascending single subcutaneous (s.c.) doses of VAY736 in RA patients
- To assess the absolute bioavailability of the s.c. route of administration

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Part 3

- To evaluate the safety and tolerability of repeated s.c. administration of a fixed 60 mg dose of VAY736 in RA patients
- To assess the pharmacokinetics (PK) of multiple s.c. doses of VAY736.
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**Secondary objective(s)**

Part 1

- To assess the PK of ascending single i.v. doses of VAY736 in RA patients
- To assess the pharmacodynamics (PD) (B-cell depletion/recovery) of ascending single i.v. doses of VAY736 in RA patients
- To assess the immunogenicity of ascending single i.v. doses of VAY736 in RA patients

Part 2

- To assess the PK of ascending single s.c. doses of VAY736 in RA patients
- To assess the PD (B-cell depletion/recovery) of ascending single s.c. doses of VAY736 in RA patients
- To assess the immunogenicity of ascending single s.c. doses of VAY736 in RA patients

Part 3

- To assess the absolute bioavailability of repeated s.c. dosing of VAY736 in RA patients
    - To assess the PD (B cell depletion/recovery) of repeated s.c. doses of VAY736 in RA patients
    - To assess the immunogenicity of repeated s.c. doses of VAY736 in RA patients

**Test Product (s), Dose(s), and Mode(s) of Administration**

- Part 1: single, escalating doses of VAY736 administered i.v. The ten dose levels were 0.0003, 0.001, 0.003, 0.01, 0.03, 0.1, 0.3, 1.0, 3.0 and 10 mg/kg.
- Part 2: single, escalating doses of VAY736 administered s.c. The dose levels were 0.6 mg/kg and 2 mg/kg.

- Part 3: multiple fixed doses of VAY736 administered s.c. The VAY736 dose level was 60 mg s.c. every two weeks.

## Statistical Methods

### Analysis of primary variable

Safety and tolerability were assessed for all parts of the study based on vital signs, ECG, laboratory evaluations and AEs. No formal statistical estimation or hypothesis testing was performed. All safety data were listed by treatment group, patient, and visit/time, and if ranges were available, abnormalities were flagged. Summary statistics were provided by treatment group and visit/time.

Absolute bioavailability was assessed with data from Parts 1 and 2. The absolute bioavailability estimate was determined from the ratio of the dose-normalized s.c. AUCinf over i.v. (or AUClast if AUCinf was not available). This was calculated separately for 0.6 mg/kg and 2 mg/kg dose levels, as the difference between mean log-transformed dose-normalized AUCinf values and back transformed to give the ratio on the original scale. Confidence intervals of 95% were also presented.

Descriptive summaries were provided for all PK concentrations and PK parameters in Part 3. Descriptive statistics of PK parameters included mean (arithmetic and geometric), SD, and CV (and geometric coefficient of variation [CV%]), median, minimum and maximum. An exception to this was Tmax where median, minimum and maximum were presented.

### Analyses of secondary variables:

### Pharmacodynamics

Part 1:

The effect of VAY736 on circulating CD19+ B-cells at Day 14 was explored using a linear effects model with dose as a fixed effect. Data was summarized using descriptive summary statistics for each dose of VAY736 and for placebo. Maximum depletion of CD19+ B-cells was compared between doses using a linear model with dose as a fixed effect. Estimates of the

difference between each dose of VAY736 and placebo were presented together with the associated 95% confidence interval. Data from placebo patients from all cohorts were pooled for analysis.

A descriptive summary of B-cell recovery was provided. B-cell recovery was defined as the time to return of ≥0.8 × baseline CD19+ B-cells or within lower limit of normal (whichever happens first). For patients who always remained within lower limit of normal the criteria taken was 0.8 × baseline.

Part 2:

As in Part 1, time to CD19+B-cell recovery was defined as ≥80% of the baseline or ≥80 cells/µL. The latter criterion was later reviewed and changed to ≥50 cells/µL.

Part 3:

Data on circulating CD19+ B-cells were listed. The clinical efficacy data collected in Part 3 was listed and summarized.

Pharmacokinetic assessments: In Parts 1 and 2, descriptive statistics was provided for all PK concentrations and PK parameters.

**Immunogenicity:**

All positive immunogenicity results in Parts 1, 2 and 3 were listed by patient and visit/time.

**Study Population: Key Inclusion/Exclusion Criteria**

**Inclusion criteria**

- Active disease despite methotrexate treatment 5 to 20 mg/week for Parts 1 and 2; methotrexate treatment 5 to 20 mg/week for Part 3

- Fulfilled 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA for Part 1 and Part 2. For Part 3, fulfilled 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria and/or 1987 American College of Rheumatology (ACR) classification criteria for RA
- Methotrexate ≥ 16 weeks, stable dose ≥ 8 weeks

**Exclusion criteria**

- Previous treatment with a B cell-depleting biologic agent
- Autoimmune disease other than RA except concurrent Sjögren's syndrome
- Adult juvenile rheumatoid arthritis
- ARA functional class IV disease of ACR Revised Steinbrocker Classification

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## Participant Flow Table

**Patient disposition - n (percent) of patients (All patients) - Part 1**

| | Placebo N=10 n (%) | VAY736 0.0003 mg/kg N=3 n (%) | VAY736 0.001 mg/kg N=3 n (%) | VAY736 0.003 mg/kg N=3 n (%) | VAY736 0.01 mg/kg N=4 n (%) | VAY736 0.03 mg/kg N=3 n (%) | VAY736 0.1 mg/kg N=3 n (%) | VAY736 0.3 mg/kg N=3 n (%) | VAY736 1 mg/kg N=3 n (%) | VAY736 3 mg/kg N=3 n (%) | VAY736 10 mg/kg N=3 n (%) | Total N=41 n (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patients | | | | | | | | | | | | |
| Completed | 10 (100.0) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 4 (100.0) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 2 (66.7) | 3 (100.0) | 3 (100.0) | 40 (97.6) |
| Discontinued | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Main cause of discontinuation | | | | | | | | | | | | |
| Administrative problems | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 1 (2.4) |

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**Patient disposition - n (percent) of patients (All patients) - Part 2**

| | VAY736 0.6mg/kg N=6 n (%) | VAY736 2mg/kg N=6 n (%) | Total N=12 n (%) |
|---|---|---|---|
| **Patients** | | | |
| Completed | 2 (33.3) | 4 (66.7) | 6 (50.0) |
| Discontinued | 4 (66.7) | 2 (33.3) | 6 (50.0) |
| | | | |
| Main cause of discontinuation | | | |
| Administrative problems | 4 (66.7) | 2 (33.3) | 6 (50.0) |

**Patient disposition - n (percent) of patients (All patients) - Part 3**

| | VAY736 60mg N=12 n (%) |
|---|---|
| **Patients** | |
| Completed | 12 (100.0) |

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## Baseline Characteristics

### Demographic summary by treatment group (Safety analysis set) - Part 1

| | | Placebo N=10 | VAY736 0.0003 mg/kg N=3 | VAY736 0.001 mg/kg N=3 | VAY736 0.003 mg/kg N=3 | VAY736 0.01 mg/kg N=4 | VAY736 0.03 mg/kg N=3 | VAY736 0.1 mg/kg N=3 | VAY736 0.3 mg/kg N=3 | VAY736 1 mg/kg N=3 | VAY736 3 mg/kg N=3 | VAY736 10 mg/kg N=3 | Total N=41 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age (years) | Mean (SD) | 56.3 (4.32) | 51.3 (11.02) | 46.0 (17.35) | 47.3 (12.50) | 52.8 (2.75) | 50.0 (7.00) | 48.3 (10.50) | 58.0 (5.29) | 59.0 (8.66) | 44.3 (16.17) | 49.3 (6.66) | 52.1 (9.15) |
| | Median | 58.0 | 52.0 | 50.0 | 53.0 | 52.5 | 53.0 | 48.0 | 60.0 | 64.0 | 47.0 | 51.0 | 53.0 |
| | Range | 48, 61 | 40, 62 | 27, 61 | 33, 56 | 50, 56 | 42, 55 | 38, 59 | 52, 62 | 49, 64 | 27, 59 | 42, 55 | 27, 64 |
| Sex - n (%) | Female | 8 (80.0) | 1 (33.3) | 3 (100.0) | 1 (33.3) | 3 (75.0) | 3 (100.0) | 3 (100.0) | 2 (66.7) | 2 (66.7) | 2 (66.7) | 2 (66.7) | 30 (73.2) |
| | Male | 2 (20.0) | 2 (66.7) | 0 (0.0) | 2 (66.7) | 1 (25.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 1 (33.3) | 1 (33.3) | 1 (33.3) | 11 (26.8) |
| Race - n (%) | Caucasian | 10 (100.0) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 4 (100.0) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 41 (100.0) |
| Ethnicity - n (%) | Other | 10 (100.0) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 4 (100.0) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 41 (100.0) |
| Weight (kg) | Mean (SD) | 72.77 (14.627) | 80.40 (9.996) | 73.47 (26.896) | 78.73 (19.652) | 78.78 (20.506) | 58.07 (6.726) | 70.47 (17.550) | 68.80 (15.352) | 79.17 (13.279) | 73.63 (7.617) | 83.77 (17.043) | 74.20 (15.310) |
| | Median | 67.75 | 82.00 | 59.00 | 83.30 | 79.60 | 61.90 | 70.50 | 63.50 | 82.00 | 74.80 | 91.00 | 70.50 |
| | Range | 55.0, 98.8 | 69.7, 89.5 | 56.9, 104.5 | 57.2, 95.7 | 53.2, 102.7 | 50.3, 62.0 | 52.9, 88.0 | 56.8, 86.1 | 64.7, 90.8 | 65.5, 80.6 | 64.3, 96.0 | 50.3, 104.5 |
| Height (cm) | Mean (SD) | 168.3 (7.78) | 167.0 (9.54) | 171.3 (7.09) | 176.3 (19.04) | 169.3 (12.28) | 167.3 (4.62) | 161.0 (1.00) | 166.3 (8.62) | 165.0 (3.46) | 173.0 (12.12) | 168.7 (12.50) | 168.5 (9.12) |
| | Median | 166.5 | 172.0 | 170.0 | 175.0 | 164.5 | 170.0 | 161.0 | 168.0 | 163.0 | 166.0 | 169.0 | 167.0 |
| | Range | 156, 181 | 156, 173 | 165, 179 | 158, 196 | 161, 187 | 162, 170 | 160, 162 | 157, 174 | 163, 169 | 166, 187 | 156, 181 | 156, 196 |
| BMI (kg/m2) | Mean (SD) | 25.529 (3.6257) | 28.754 (1.0976) | 24.658 (6.9614) | 25.282 (5.2041) | 27.169 (4.4352) | 20.679 (1.3105) | 27.159 (6.6476) | 24.660 (3.2833) | 29.079 (4.9221) | 24.803 (4.0302) | 29.270 (3.8208) | 26.024 (4.3326) |
| | Median | 25.104 | 28.641 | 21.671 | 22.913 | 29.248 | 21.419 | 26.863 | 23.044 | 28.710 | 23.770 | 27.777 | 26.422 |

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| | Placebo N=10 | VAY736 0.0003 mg/kg N=3 | VAY736 0.001 mg/kg N=3 | VAY736 0.003 mg/kg N=3 | VAY736 0.01 mg/kg N=4 | VAY736 0.03 mg/kg N=3 | VAY736 0.1 mg/kg N=3 | VAY736 0.3 mg/kg N=3 | VAY736 1 mg/kg N=3 | VAY736 3 mg/kg N=3 | VAY736 10 mg/kg N=3 | Total N=41 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Range | 20.96, 30.53 | 27.72, 29.90 | 19.69, 32.61 | 21.68, 31.25 | 20.52, 29.66 | 19.17, 21.45 | 20.66, 33.95 | 22.50, 28.44 | 24.35, 34.18 | 21.39, 29.25 | 26.42, 33.61 | 19.17, 34.18 |

**Demographic summary by treatment group (Safety analysis set) - Part 2**

| | | VAY736 0.6mg/kg N=6 | VAY736 2mg/kg N=6 | Total N=12 |
|---|---|---|---|---|
| Age (years) | Mean (SD) | 50.2 (11.53) | 53.3 (6.68) | 51.8 (9.14) |
| | Median | 54.0 | 55.5 | 54.5 |
| | Range | 28, 59 | 40, 58 | 28, 59 |
| Sex - n (%) | Female | 5 (83.3) | 2 (33.3) | 7 (58.3) |
| | Male | 1 (16.7) | 4 (66.7) | 5 (41.7) |
| Race - n (%) | Black | 0 (0.0) | 1 (16.7) | 1 (8.3) |
| | Caucasian | 5 (83.3) | 5 (83.3) | 10 (83.3) |
| | Other | 1 (16.7) | 0 (0.0) | 1 (8.3) |
| Ethnicity - n (%) | Other | 6 (100.0) | 6 (100.0) | 12 (100.0) |
| Weight (kg) | Mean (SD) | 73.05 (13.886) | 79.10 (15.350) | 76.07 (14.309) |
| | Median | 74.40 | 74.30 | 74.40 |
| | Range | 53.3, 92.0 | 64.0, 98.8 | 53.3, 98.8 |
| Height (cm) | Mean (SD) | 166.5 (8.12) | 176.8 (8.18) | 171.7 (9.46) |
| | Median | 165.5 | 177.0 | 172.0 |
| | Range | 155, 178 | 166, 189 | 155, 189 |
| BMI ($kg/m^2$) | Mean (SD) | 26.253 (3.9684) | 25.106 (3.0883) | 25.680 (3.4427) |
| | Median | 27.546 | 23.593 | 25.009 |
| | Range | 20.78, 30.12 | 22.67, 30.49 | 20.78, 30.49 |

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**Demographic summary by treatment group (Safety analysis set) – Part 3**

| | | **VAY736 60mg N=12** |
|---|---|---|
| Age (years) | Mean (SD) | 52.8 (7.29) |
| | Median | 55.0 |
| | Range | 34, 60 |
| Sex - n (%) | Female | 5 (41.7) |
| | Male | 7 (58.3) |
| Race - n (%) | Caucasian | 12 (100.0) |
| Ethnicity - n (%) | Other | 12 (100.0) |
| Weight (kg) | Mean (SD) | 83.47 (12.255) |
| | Median | 81.25 |
| | Range | 65.2, 104.0 |
| Height (cm) | Mean (SD) | 175.5 (9.70) |
| | Median | 177.0 |
| | Range | 158, 190 |
| BMI ($kg/m^2$) | Mean (SD) | 27.060 (2.9681) |
| | Median | 26.745 |
| | Range | 22.49, 31.55 |

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## Summary of Efficacy

## Primary Outcome Result(s)

Refer to Safety Result section for primary outcome results.

**Statistical analysis of the bioavailability of serum VAY736 pharmacokinetic parameters (PK analysis set)**

| Parameter | Route | Dose (mg/kg) | n | Geometric LSmean 95% CI | Ratio of geometric LSmean vs intravenous | 95% CI | P-value |
|---|---|---|---|---|---|---|---|
| AUCinf (day*ug/mL) | Intravenous | 0.3 | 3 | 1.189 (0.693, 2.038) | 0.362 | (0.187, 0.701) | 0.005 |
| | Intravenous | 1 | 3 | 1.499 (0.874, 2.569) | 0.287 | (0.149, 0.556) | <.001 |
| | Intravenous | 3 | 3 | 1.193 (0.696, 2.045) | 0.361 | (0.187, 0.699) | 0.005 |
| | Intravenous | 10 | 3 | 1.361 (0.794, 2.333) | 0.316 | (0.164, 0.612) | 0.002 |
| | Subcutaneous | 0.6 | 6 | 0.431 (0.294, 0.630) | | | |
| | Intravenous | 0.3 | 3 | 1.189 (0.693, 2.038) | 0.538 | (0.278, 1.040) | 0.064 |
| | Intravenous | 1 | 3 | 1.499 (0.874, 2.569) | 0.426 | (0.220, 0.825) | 0.014 |
| | Intravenous | 3 | 3 | 1.193 (0.696, 2.045) | 0.536 | (0.277, 1.036) | 0.062 |
| | Intravenous | 10 | 3 | 1.361 (0.794, 2.333) | 0.470 | (0.243, 0.908) | 0.027 |
| | Subcutaneous | 2 | 6 | 0.639 (0.436, 0.935) | | | |

Geometric LSmean (CI), ratio of geometric LSmean, 95% CI and P-value were obtained from an analysis of variance (ANOVA)of the dose normalised and log-transformed data with route and dose as fixed effects. The estimates of geometric LSmean (CI), ratio of geometric LSmean and 95% CI have been back transformed onto the original scale.

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## PK parameters (PK analysis set) - Part 3

Compound: VAY736, Matrix: Serum-PK, Analyte: VAY736
Treatment: VAY736 60mg

| Profile day | PK collection number | | AUClast (day × µg/mL) | Cmax (µg/mL) | Tmax (h) | AUCtau (day × µg/mL) | AUCinf (day × µg/mL) | T1/2 (day) |
|---|---|---|---|---|---|---|---|---|
| 1 | 1 | n | 12 | 12 | 12 | 12 | | |
| | | Mean (SD) | 23.7 (8.15) | 2.75 (1.06) | | 23.7 (8.16) | | |
| | | CV% mean | 34.4 | 38.7 | | 34.4 | | |
| | | Geo-mean | 22.3 | 2.54 | | 22.3 | | |
| | | CV% geo-mean | 39.4 | 46.1 | | 39.4 | | |
| | | Median | 22.3 | 2.68 | 71.7 | 22.3 | | |
| | | [Min; Max] | [10.2; 36.2] | [1.15; 4.37] | [71.4; 145] | [10.2; 36.2] | | |
| 71 | 6 | n | 11 | 11 | 11 | 11 | 11 | 11 |
| | | Mean (SD) | 64.3 (36.5) | 4.61 (1.72) | | 41.8 (17.5) | 65.5 (36.3) | 8.78 (2.94) |
| | | CV% mean | 56.8 | 37.4 | | 41.9 | 55.4 | 33.5 |
| | | Geo-mean | 56.3 | 4.30 | | 38.6 | 57.8 | 8.38 |
| | | CV% geo-mean | 56.8 | 42.0 | | 43.1 | 54.3 | 32.4 |
| | | Median | 50.8 | 4.39 | 71.8 | 35.4 | 51.1 | 7.89 |
| | | [Min; Max] | [26.6; 130] | [2.18; 7.01] | [71.0; 80.7] | [20.2; 68.5] | [29.4; 131] | [5.17; 14.7] |

CV% mean = Coefficient of variation (%) = sd/mean × 100
CV% geo mean = sqrt (exp (variance for log transformed data) - 1) × 100

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**Summary of serum Ctrough during treatment period (PK analysis set) - Part 3**

Compound: VAY736, Matrix: Serum-PK, Analyte: VAY736
Treatment: VAY736 60mg

| Profile day | PK collection number | | Ctrough (ug/mL) |
|---|---|---|---|
| 15 | 2 | n | 12 |
| | | Mean (SD) | 0.745 (0.341) |
| | | CV% mean | 45.8 |
| | | Geo-mean | 0.676 |
| | | CV% geo-mean | 49.6 |
| | | Median | 0.676 |
| | | [Min; Max] | [0.262; 1.43] |
| 29 | 3 | n | 12 |
| | | Mean (SD) | 1.22 (0.584) |
| | | CV% mean | 47.7 |
| | | Geo-mean | 1.11 |
| | | CV% geo-mean | 49.0 |
| | | Median | 0.994 |
| | | [Min; Max] | [0.552; 2.27] |
| 43 | 4 | n | 12 |
| | | Mean (SD) | 1.29 (0.659) |
| | | CV% mean | 51.0 |
| | | Geo-mean | 1.15 |
| | | CV% geo-mean | 53.8 |
| | | Median | 1.01 |

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Compound: VAY736, Matrix: Serum-PK, Analyte: VAY736
Treatment: VAY736 60mg

| Profile day | PK collection number | | Ctrough (ug/mL) |
|---|---|---|---|
| | | [Min; Max] | [0.596; 2.46] |
| 57 | 5 | n | 11 |
| | | Mean (SD) | 1.34 (0.721) |
| | | CV% mean | 53.6 |
| | | Geo-mean | 1.19 |
| | | CV% geo-mean | 53.1 |
| | | Median | 0.976 |
| | | [Min; Max] | [0.710; 2.78] |
| 71 | 6 | n | 11 |
| | | Mean (SD) | 1.40 (0.824) |
| | | CV% mean | 59.0 |
| | | Geo-mean | 1.22 |
| | | CV% geo-mean | 56.4 |
| | | Median | 0.969 |
| | | [Min; Max] | [0.668; 3.10] |
| 85 | 6 | n | 11 |
| | | Mean (SD) | 1.47 (0.845) |
| | | CV% mean | 57.6 |
| | | Geo-mean | 1.29 |
| | | CV% geo-mean | 55.6 |
| | | Median | 1.08 |

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| Compound: VAY736, Matrix: Serum-PK, Analyte: VAY736<br>Treatment: VAY736 60mg | | |
|---|---|---|
| **Profile day** | **PK collection number** | **Ctrough (ug/mL)** |
| | [Min; Max] | [0.681; 3.28] |

CV% mean = Coefficient of variation (%) = sd/mean*100
CV% geo mean = sqrt(exp(variance for log transformed data)-1) * 100

## Secondary Outcome Result(s)

### Pharmacokinetics:

#### PK parameters (PK analysis set) - Part 1

| **Compound: VAY736, Matrix: Serum-PK, Analyte: VAY736** | | | | | |
|---|---|---|---|---|---|
| **Treatment** | **PK collection number** | | **AUClast (day × µg/mL)** | **Cmax (µg/mL)** | **Tmax (h)** |
| VAY736 0.003 mg/kg | 1 | n | 1 | 1 | 1 |
| | | Mean (SD) | 0.00330 | 0.0389 | |
| | | CV% mean | | | |
| | | Geo-mean | 0.00330 | 0.0389 | |
| | | CV% geo-mean | | | |
| | | Median | 0.00330 | 0.0389 | 4.07 |
| | | [Min; Max] | [0.00330; 0.00330] | [0.0389; 0.0389] | [4.07; 4.07] |

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| Compound: VAY736, Matrix: Serum-PK, Analyte: VAY736 | | | | | |
|---|---|---|---|---|---|
| **Treatment** | **PK collection number** | | **AUClast (day × µg/mL)** | **Cmax (µg/mL)** | **Tmax (h)** |
| VAY736 0.01 mg/kg | 1 | n | 2 | 3 | 3 |
| | | Mean (SD) | 0.0919 (0.125) | 0.0979 (0.0564) | |
| | | CV% mean | 136.6 | 57.7 | |
| | | Geo-mean | 0.0238 | 0.0831 | |
| | | CV% geo-mean | 6033.3 | 89.3 | |
| | | Median | 0.0919 | 0.116 | 4.37 |
| | | [Min; Max] | [0.00315; 0.181] | [0.0346; 0.143] | [4.37; 4.38] |
| VAY736 0.03 mg/kg | 1 | n | 3 | 3 | 3 |
| | | Mean (SD) | 1.18 (0.370) | 0.534 (0.0448) | |
| | | CV% mean | 31.3 | 8.4 | |
| | | Geo-mean | 1.14 | 0.532 | |
| | | CV% geo-mean | 31.9 | 8.4 | |
| | | Median | 1.12 | 0.528 | 4.38 |
| | | [Min; Max] | [0.849; 1.58] | [0.492; 0.581] | [4.37; 4.42] |
| VAY736 0.1 mg/kg | 1 | n | 3 | 3 | 3 |
| | | Mean (SD) | 8.09 (1.92) | 2.23 (0.418) | |
| | | CV% mean | 23.7 | 18.7 | |
| | | Geo-mean | 7.95 | 2.21 | |
| | | CV% geo-mean | 23.3 | 19.5 | |
| | | Median | 7.54 | 2.29 | 4.50 |
| | | [Min; Max] | [6.51; 10.2] | [1.79; 2.62] | [4.38; 4.62] |
| VAY736 0.3 mg/kg | 1 | n | 3 | 3 | 3 |

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| Compound: VAY736, Matrix: Serum-PK, Analyte: VAY736 | | | | | |
|---|---|---|---|---|---|
| **Treatment** | **PK collection number** | | **AUClast (day × µg/mL)** | **Cmax (µg/mL)** | **Tmax (h)** |
| | | Mean (SD) | 24.7 (9.64) | 5.53 (0.176) | |
| | | CV% mean | 39.0 | 3.2 | |
| | | Geo-mean | 23.6 | 5.52 | |
| | | CV% geo-mean | 37.7 | 3.2 | |
| | | Median | 20.1 | 5.58 | 4.38 |
| | | [Min; Max] | [18.2; 35.8] | [5.33; 5.67] | [4.20; 4.47] |
| VAY736 1 mg/kg | 1 | n | 3 | 3 | 3 |
| | | Mean (SD) | 117 (19.9) | 20.7 (1.31) | |
| | | CV% mean | 17.0 | 6.3 | |
| | | Geo-mean | 116 | 20.7 | |
| | | CV% geo-mean | 16.6 | 6.4 | |
| | | Median | 110 | 21.3 | 4.45 |
| | | [Min; Max] | [102; 140] | [19.2; 21.6] | [4.37; 4.45] |
| VAY736 3 mg/kg | 1 | n | 3 | 3 | 3 |
| | | Mean (SD) | 270 (78.1) | 58.3 (13.9) | |
| | | CV% mean | 28.9 | 23.9 | |
| | | Geo-mean | 263 | 57.2 | |
| | | CV% geo-mean | 28.0 | 24.1 | |
| | | Median | 238 | 56.2 | 4.43 |
| | | [Min; Max] | [214; 359] | [45.6; 73.2] | [4.42; 4.58] |
| VAY736 10 mg/kg | 1 | n | 3 | 3 | 3 |
| | | Mean (SD) | 1150 (288) | 242 (35.8) | |

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| Compound: VAY736, Matrix: Serum-PK, Analyte: VAY736 | | | | | |
|---|---|---|---|---|---|
| **Treatment** | **PK collection number** | | **AUClast (day × µg/mL)** | **Cmax (µg/mL)** | **Tmax (h)** |
| | | CV% mean | 25.0 | 14.8 | |
| | | Geo-mean | 1130 | 240 | |
| | | CV% geo-mean | 24.8 | 15.6 | |
| | | Median | 1080 | 258 | 4.42 |
| | | [Min; Max] | [906; 1470] | [201; 267] | [4.38; 4.50] |

CV% mean = Coefficient of variation (%) = sd/mean × 100
CV% geo mean = sqrt (exp(variance for log transformed data) - 1 × 100

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**PK parameters (PK analysis set) - Part 2**

**Compound: VAY736, Matrix: Serum-PK, Analyte: VAY736**

| Treatment: | PK collection number | | AUClast (day × µg/mL) | Cmax (µg/mL) | Tmax (h) |
|---|---|---|---|---|---|
| 0.6 mg/kg VAY736 | 1 | n | 6 | 6 | 6 |
| | | Mean (SD) | 18.7 (5.04) | 1.33 (0.369) | |
| | | CV% mean | 26.9 | 27.6 | |
| | | Geo-mean | 18.0 | 1.28 | |
| | | CV% geo-mean | 33.0 | 36.3 | |
| | | Median | 19.5 | 1.39 | 72.3 |
| | | [Min; Max] | [9.84; 24.0] | [0.639; 1.70] | [71.2; 144] |
| 2 mg/kg VAY736 | 1 | n | 6 | 6 | 6 |
| | | Mean (SD) | 109 (46.5) | 8.24 (2.78) | |
| | | CV% mean | 42.6 | 33.7 | |
| | | Geo-mean | 98.2 | 7.72 | |
| | | CV% geo-mean | 60.9 | 45.1 | |
| | | Median | 120 | 8.35 | 71.8 |
| | | [Min; Max] | [35.4; 164] | [3.38; 11.9] | [70.4; 145] |

CV% mean = Coefficient of variation (%) = sd/mean × 100
CV% geo mean = sqrt (exp (variance for log transformed data) - 1) × 100

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## Pharmacodynamics - B-cell depletion/recovery

### Summary of B cell count data (PD analysis set) – Part 1 (a)

| Visit | Scheduled timepoint | | Placebo B cells (cells/uL) | Treatment: VAY736 0.0003mg/kg B cells (cells/uL) | Treatment: VAY736 0.001mg/kg B cells (cells/uL) | Treatment: VAY736 0.003mg/kg B cells (cells/uL) | Treatment: VAY736 0.01mg/kg B cells (cells/uL) |
|---|---|---|---|---|---|---|---|
| BAS | | n | 10 | 3 | 3 | 3 | 4 |
| | | Mean (SD) | 552.60 (301.019) | 632.67 (225.469) | 300.67 (167.130) | 638.33 (495.980) | 369.00 (119.211) |
| | | CV% mean | 54.5 | 35.6 | 55.6 | 77.7 | 32.3 |
| | | Geo-mean | 483.98 | 608.65 | 271.65 | 531.33 | 353.03 |
| | | CV% geo-mean | 58.9 | 34.1 | 59.2 | 81.5 | 36.6 |
| | | Median | 432.50 | 505.00 | 251.00 | 358.00 | 382.50 |
| | | [Min; Max] | [201.0; 1139.0] | [500.0; 893.0] | [164.0; 487.0] | [346.0; 1211.0] | [221.0; 490.0] |
| D1 | 4 | n | 10 | 3 | 3 | 3 | 3 |
| | | Mean (SD) | 524.70 (220.018) | 385.33 (127.123) | 62.00 (37.162) | 353.33 (421.635) | 170.67 (114.910) |
| | | CV% mean | 41.9 | 33.0 | 59.9 | 119.3 | 67.3 |
| | | Geo-mean | 485.03 | 369.71 | 52.81 | 207.89 | 143.14 |
| | | CV% geo-mean | 43.9 | 37.6 | 86.2 | 198.8 | 87.7 |
| | | Median | 494.00 | 415.00 | 66.00 | 151.00 | 154.00 |
| | | [Min; Max] | [250.0; 929.0] | [246.0; 495.0] | [23.0; 97.0] | [71.0; 838.0] | [65.0; 293.0] |
| D2 | 24 | n | 10 | 3 | 3 | 3 | 4 |
| | | Mean (SD) | 495.80 (196.336) | 424.67 (133.822) | 136.00 (65.643) | 235.00 (286.676) | 46.25 (32.004) |
| | | CV% mean | 39.6 | 31.5 | 48.3 | 122.0 | 69.2 |

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| Visit | Scheduled timepoint | | Placebo B cells (cells/uL) | Treatment: VAY736 0.0003mg/kg B cells (cells/uL) | Treatment: VAY736 0.001mg/kg B cells (cells/uL) | Treatment: VAY736 0.003mg/kg B cells (cells/uL) | Treatment: VAY736 0.01mg/kg B cells (cells/uL) |
|---|---|---|---|---|---|---|---|
| | | Geo-mean | 462.14 | 410.86 | 124.03 | 139.71 | 37.06 |
| | | CV% geo-mean | 41.3 | 32.3 | 59.2 | 183.1 | 94.7 |
| | | Median | 460.00 | 403.00 | 141.00 | 73.00 | 44.50 |
| | | [Min; Max] | [246.0; 869.0] | [303.0; 568.0] | [68.0; 199.0] | [66.0; 566.0] | [16.0; 80.0] |
| D5 | 96 | n | 10 | 3 | 3 | 3 | 4 |
| | | Mean (SD) | 531.60 (243.014) | 611.67 (281.287) | 181.33 (111.881) | 351.67 (332.064) | 65.25 (32.408) |
| | | CV% mean | 45.7 | 46.0 | 61.7 | 94.4 | 49.7 |
| | | Geo-mean | 481.64 | 566.30 | 160.56 | 256.27 | 59.13 |
| | | CV% geo-mean | 50.5 | 52.3 | 65.2 | 127.3 | 55.4 |
| | | Median | 438.00 | 597.00 | 140.00 | 222.00 | 60.50 |
| | | [Min; Max] | [217.0; 921.0] | [338.0; 900.0] | [96.0; 308.0] | [104.0; 729.0] | [38.0; 102.0] |
| D7 | | n | 10 | 3 | 3 | 3 | 4 |
| | | Mean (SD) | 499.90 (204.635) | 585.67 (252.694) | 237.00 (161.298) | 382.00 (356.711) | 71.00 (21.572) |
| | | CV% mean | 40.9 | 43.1 | 68.1 | 93.4 | 30.4 |
| | | Geo-mean | 464.20 | 544.80 | 204.79 | 274.10 | 68.18 |
| | | CV% geo-mean | 42.3 | 51.3 | 72.2 | 137.4 | 35.3 |
| | | Median | 502.50 | 614.00 | 170.00 | 263.00 | 74.00 |
| | | [Min; Max] | [265.0; 892.0] | [320.0; 823.0] | [120.0; 421.0] | [100.0; 783.0] | [42.0; 94.0] |
| D14 | | n | 10 | 3 | 3 | 3 | 4 |
| | | Mean (SD) | 440.70 (212.135) | 604.67 (279.786) | 269.00 (220.823) | 316.67 (280.921) | 71.75 (30.945) |
| | | CV% mean | 48.1 | 46.3 | 82.1 | 88.7 | 43.1 |

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| Visit | Scheduled timepoint | | Placebo B cells (cells/uL) | Treatment: VAY736 0.0003mg/kg B cells (cells/uL) | Treatment: VAY736 0.001mg/kg B cells (cells/uL) | Treatment: VAY736 0.003mg/kg B cells (cells/uL) | Treatment: VAY736 0.01mg/kg B cells (cells/uL) |
|---|---|---|---|---|---|---|---|
| | | Geo-mean | 399.68 | 553.44 | 216.91 | 245.61 | 66.24 |
| | | CV% geo-mean | 48.5 | 58.5 | 92.3 | 103.5 | 50.6 |
| | | Median | 340.50 | 661.00 | 170.00 | 187.00 | 72.50 |
| | | [Min; Max] | [209.0; 863.0] | [301.0; 852.0] | [115.0; 522.0] | [124.0; 639.0] | [36.0; 106.0] |

CV% = coefficient of variation (%)=sd/mean*100;
CV% geo-mean=(sqrt (exp (variance for log transformed data)-1))*100

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**Summary of B cell count data (PD analysis set) – Part 1 (b)**

| Visit | Scheduled timepoint | | Treatment: VAY736 0.03mg/kg B cells (cells/uL) | Treatment: VAY736 0.1mg/kg B cells (cells/uL) | Treatment: VAY736 0.3mg/kg B cells (cells/uL) | Treatment: VAY736 1 mg/kg B cells (cells/uL) | Treatment: VAY736 3 mg/kg B cells (cells/uL) |
|---|---|---|---|---|---|---|---|
| BAS | | n | 3 | 3 | 3 | 3 | 3 |
| | | Mean (SD) | 767.33 (471.186) | 388.00 (76.864) | 579.67 (261.117) | 645.00 (683.347) | 646.00 (175.419) |
| | | CV% mean | 61.4 | 19.8 | 45.0 | 105.9 | 27.2 |
| | | Geo-mean | 631.54 | 382.49 | 533.41 | 447.94 | 631.41 |
| | | CV% geo-mean | 102.2 | 21.4 | 56.3 | 132.8 | 26.1 |
| | | Median | 915.00 | 422.00 | 633.00 | 259.00 | 558.00 |
| | | [Min; Max] | [240.0; 1147.0] | [300.0; 442.0] | [296.0; 810.0] | [242.0; 1434.0] | [532.0; 848.0] |
| D1 | 4 | n | 3 | 3 | 3 | 3 | 3 |
| | | Mean (SD) | 177.00 (84.788) | 26.33 (10.970) | 32.67 (9.292) | 11.00 (7.550) | 42.67 (12.503) |
| | | CV% mean | 47.9 | 41.7 | 28.4 | 68.6 | 29.3 |
| | | Geo-mean | 160.53 | 24.50 | 31.66 | 8.65 | 41.54 |
| | | CV% geo-mean | 62.4 | 52.2 | 32.5 | 119.1 | 28.3 |
| | | Median | 197.00 | 30.00 | 37.00 | 12.00 | 37.00 |
| | | [Min; Max] | [84.0; 250.0] | [14.0; 35.0] | [22.0; 39.0] | [3.0; 18.0] | [34.0; 57.0] |
| D2 | 24 | n | 3 | 3 | 3 | 3 | 3 |
| | | Mean (SD) | 49.67 (29.366) | 32.00 (10.583) | 66.33 (41.405) | 33.67 (14.154) | 19.00 (7.000) |
| | | CV% mean | 59.1 | 33.1 | 62.4 | 42.0 | 36.8 |
| | | Geo-mean | 41.32 | 30.65 | 55.07 | 31.91 | 17.98 |
| | | CV% geo-mean | 98.5 | 38.7 | 97.0 | 40.5 | 44.8 |

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| Visit | Scheduled timepoint | | Treatment: VAY736 0.03mg/kg B cells (cells/uL) | Treatment: VAY736 0.1mg/kg B cells (cells/uL) | Treatment: VAY736 0.3mg/kg B cells (cells/uL) | Treatment: VAY736 1 mg/kg B cells (cells/uL) | Treatment: VAY736 3 mg/kg B cells (cells/uL) |
|---|---|---|---|---|---|---|---|
| | | Median | 63.00 | 36.00 | 73.00 | 26.00 | 22.00 |
| | | [Min; Max] | [16.0; 70.0] | [20.0; 40.0] | [22.0; 104.0] | [25.0; 50.0] | [11.0; 24.0] |
| D5 | 96 | n | 3 | 3 | 3 | 3 | 3 |
| | | Mean (SD) | 76.00 (38.432) | 41.00 (29.715) | 67.33 (36.474) | 64.67 (21.502) | 14.67 (7.371) |
| | | CV% mean | 50.6 | 72.5 | 54.2 | 33.3 | 50.3 |
| | | Geo-mean | 67.73 | 34.76 | 58.84 | 61.99 | 13.54 |
| | | CV% geo-mean | 69.8 | 77.6 | 77.4 | 38.1 | 51.0 |
| | | Median | 88.00 | 28.00 | 77.00 | 70.00 | 12.00 |
| | | [Min; Max] | [33.0; 107.0] | [20.0; 75.0] | [27.0; 98.0] | [41.0; 83.0] | [9.0; 23.0] |
| D7 | | n | 3 | 3 | 3 | 3 | 3 |
| | | Mean (SD) | 46.33 (32.868) | 37.67 (21.221) | 77.67 (56.128) | 53.67 (12.858) | 13.33 (3.055) |
| | | CV% mean | 70.9 | 56.3 | 72.3 | 24.0 | 22.9 |
| | | Geo-mean | 35.16 | 34.18 | 63.28 | 52.53 | 13.08 |
| | | CV% geo-mean | 136.2 | 56.3 | 97.6 | 26.4 | 24.6 |
| | | Median | 52.00 | 28.00 | 68.00 | 59.00 | 14.00 |
| | | [Min; Max] | [11.0; 76.0] | [23.0; 62.0] | [27.0; 138.0] | [39.0; 63.0] | [10.0; 16.0] |
| D14 | | n | 3 | 3 | 3 | 3 | 3 |
| | | Mean (SD) | 30.67 (19.218) | 16.00 (6.083) | 32.00 (26.907) | 20.67 (8.386) | 6.00 (3.000) |
| | | CV% mean | 62.7 | 38.0 | 84.1 | 40.6 | 50.0 |
| | | Geo-mean | 25.37 | 15.07 | 24.60 | 19.26 | 5.45 |
| | | CV% geo-mean | 98.6 | 47.0 | 114.0 | 51.6 | 60.1 |

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| Visit | Scheduled timepoint | | Treatment: VAY736 0.03mg/kg B cells (cells/uL) | Treatment: VAY736 0.1mg/kg B cells (cells/uL) | Treatment: VAY736 0.3mg/kg B cells (cells/uL) | Treatment: VAY736 1 mg/kg B cells (cells/uL) | Treatment: VAY736 3 mg/kg B cells (cells/uL) |
|---|---|---|---|---|---|---|---|
| | | Median | 34.00 | 19.00 | 24.00 | 25.00 | 6.00 |
| | | [Min; Max] | [10.0; 48.0] | [9.0; 20.0] | [10.0; 62.0] | [11.0; 26.0] | [3.0; 9.0] |

CV% = coefficient of variation (%)=sd/mean*100;
CV% geo-mean=(sqrt (exp (variance for log transformed data)-1))*100

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**Summary of B cell count data (PD analysis set) – Part 1 (c)**

| Visit | Scheduled timepoint | | Treatment: VAY736 10 mg/kg B cells (cells/uL) |
|---|---|---|---|
| BAS | | n | 3 |
| | | Mean (SD) | 670.40 (487.530) |
| | | CV% mean | 72.7 |
| | | Geo-mean | 542.76 |
| | | CV% geo-mean | 100.3 |
| | | Median | 593.00 |
| | | [Min; Max] | [226.2; 1192.0] |
| D1 | 4 | n | 3 |
| | | Mean (SD) | 105.33 (78.360) |
| | | CV% mean | 74.4 |
| | | Geo-mean | 77.71 |
| | | CV% geo-mean | 148.3 |
| | | Median | 114.00 |
| | | [Min; Max] | [23.0; 179.0] |
| D2 | 24 | n | 3 |
| | | Mean (SD) | 47.97 (29.661) |
| | | CV% mean | 61.8 |
| | | Geo-mean | 41.36 |
| | | CV% geo-mean | 78.5 |
| | | Median | 45.00 |
| | | [Min; Max] | [19.9; 79.0] |
| D5 | 96 | n | 3 |

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| Visit | Scheduled timepoint | | Treatment: VAY736 10 mg/kg B cells (cells/uL) |
|---|---|---|---|
| | | Mean (SD) | 52.13 (51.717) |
| | | CV% mean | 99.2 |
| | | Geo-mean | 36.54 |
| | | CV% geo-mean | 140.4 |
| | | Median | 31.40 |
| | | [Min; Max] | [14.0; 111.0] |
| D7 | | n | 3 |
| | | Mean (SD) | 40.63 (45.807) |
| | | CV% mean | 112.7 |
| | | Geo-mean | 24.96 |
| | | CV% geo-mean | 190.0 |
| | | Median | 20.90 |
| | | [Min; Max] | [8.0; 93.0] |
| D14 | | n | 3 |
| | | Mean (SD) | 21.93 (24.479) |
| | | CV% mean | 111.6 |
| | | Geo-mean | 13.92 |
| | | CV% geo-mean | 171.8 |
| | | Median | 10.80 |
| | | [Min; Max] | [5.0; 50.0] |

CV% = coefficient of variation (%)=sd/mean*100;
CV% geo-mean=(sqrt (exp (variance for log transformed data)-1))*100

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**Summary statistics of duration (in days) of B cell recovery from baseline (PD analysis set) – Part 1**

| | Placebo N=10 | VAY736 0.0003 mg/kg N=3 | VAY736 0.001 mg/kg N=3 | VAY736 0.003 mg/kg N=3 | VAY736 0.01 mg/kg N=4 | VAY736 0.03 mg/kg N=3 | VAY736 0.1 mg/kg N=3 | VAY736 0.3 mg/kg N=3 | VAY736 1 mg/kg N=3 | VAY736 3 mg/kg N=3 | VAY736 10 mg/kg N=3 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| n | 10 | 3 | 3 | 3 | 4 | 3 | 3 | 3 | 3 | 3 | 3 |
| Mean (Days) | 33 | 55 | 13 | 16 | 46 | 69 | 177 | 390 | 314 | 419 | 231 |
| SD (Days) | 10 | 12 | 18 | 21 | 25 | 34 | 96 | 422 | 30 | 359 | 43 |
| minimum | 27 | 41 | 1 | 4 | 28 | 34 | 111 | 72 | 280 | 181 | 188 |
| median | 27 | 62 | 4 | 4 | 38 | 69 | 132 | 229 | 328 | 244 | 232 |
| maximum | 56 | 63 | 34 | 41 | 83 | 103 | 287 | 868 | 335 | 832 | 273 |

Criteria used: time to return to >= 80 cells/uL (for patients with >= 80 cells/uL at baseline) or at least 80% of baseline levels (for patients with < 80 cells/uL at baseline)

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**Summary of B cell count data (PD analysis set) – Part 2 (a)**

| Treatment: VAY736 0.6mg/kg | | | |
|---|---|---|---|
| **Visit** | **Scheduled timepoint** | | **B cells (cells/uL)** |
| BAS | | n | 5 |
| | | Mean (SD) | 170.80 (80.884) |
| | | CV% mean | 47.4 |
| | | Geo-mean | 154.83 |
| | | CV% geo-mean | 54.0 |
| | | Median | 161.00 |
| | | [Min; Max] | [83.0; 271.0] |
| D2 | 24 | n | 6 |
| | | Mean (SD) | 7.97 (4.877) |
| | | CV% mean | 61.2 |
| | | Geo-mean | 6.07 |
| | | CV% geo-mean | 120.7 |
| | | Median | 8.50 |
| | | [Min; Max] | [1.1; 14.0] |
| D4 | 72 | n | 5 |
| | | Mean (SD) | 13.84 (9.505) |
| | | CV% mean | 68.7 |
| | | Geo-mean | 11.63 |
| | | CV% geo-mean | 72.6 |
| | | Median | 12.60 |
| | | [Min; Max] | [5.8; 29.5] |

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| Treatment: VAY736 0.6mg/kg | | | |
|---|---|---|---|
| **Visit** | **Scheduled timepoint** | | **B cells (cells/uL)** |
| D7 | 144 | n | 5 |
| | | Mean (SD) | 12.64 (11.832) |
| | | CV% mean | 93.6 |
| | | Geo-mean | 7.13 |
| | | CV% geo-mean | 287.5 |
| | | Median | 10.80 |
| | | [Min; Max] | [0.6; 32.1] |
| D14 | 312 | n | 6 |
| | | Mean (SD) | 4.22 (3.400) |
| | | CV% mean | 80.6 |
| | | Geo-mean | 3.53 |
| | | CV% geo-mean | 63.6 |
| | | Median | 3.05 |
| | | [Min; Max] | [2.2; 11.1] |
| EOS | | n | 6 |
| | | Mean (SD) | 61.33 (34.029) |
| | | CV% mean | 55.5 |
| | | Geo-mean | 50.55 |
| | | CV% geo-mean | 89.0 |
| | | Median | 66.95 |
| | | [Min; Max] | [13.4; 98.3] |

CV% = coefficient of variation (%)=sd/mean*100;
CV% geo-mean=(sqrt (exp (variance for log transformed data)-1))*100

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**Summary of B cell count data (PD analysis set) – Part 2 (b)**

| Treatment: VAY736 2mg/kg | | | |
|---|---|---|---|
| **Visit** | **Scheduled timepoint** | | **B cells (cells/uL)** |
| BAS | | n | 5 |
| | | Mean (SD) | 138.18 (57.206) |
| | | CV% mean | 41.4 |
| | | Geo-mean | 129.00 |
| | | CV% geo-mean | 43.2 |
| | | Median | 110.00 |
| | | [Min; Max] | [80.9; 207.0] |
| D2 | 24 | n | 6 |
| | | Mean (SD) | 5.58 (2.794) |
| | | CV% mean | 50.0 |
| | | Geo-mean | 4.99 |
| | | CV% geo-mean | 56.9 |
| | | Median | 5.15 |
| | | [Min; Max] | [2.7; 9.3] |
| D4 | 72 | n | 6 |
| | | Mean (SD) | 8.38 (5.779) |
| | | CV% mean | 68.9 |
| | | Geo-mean | 6.79 |
| | | CV% geo-mean | 85.3 |
| | | Median | 8.10 |
| | | [Min; Max] | [2.3; 18.6] |
| D7 | 144 | n | 5 |
| | | Mean (SD) | 8.98 (3.885) |

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| Treatment: VAY736 2mg/kg | | | |
|---|---|---|---|
| **Visit** | **Scheduled timepoint** | | **B cells (cells/uL)** |
| | | CV% mean | 43.3 |
| | | Geo-mean | 8.22 |
| | | CV% geo-mean | 52.5 |
| | | Median | 8.50 |
| | | [Min; Max] | [3.8; 14.4] |
| D14 | 312 | n | 6 |
| | | Mean (SD) | 2.57 (1.189) |
| | | CV% mean | 46.3 |
| | | Geo-mean | 2.28 |
| | | CV% geo-mean | 61.8 |
| | | Median | 2.75 |
| | | [Min; Max] | [0.9; 4.1] |
| EOS | | n | 5 |
| | | Mean (SD) | 56.44 (55.492) |
| | | CV% mean | 98.3 |
| | | Geo-mean | 21.77 |
| | | CV% geo-mean | 665.9 |
| | | Median | 55.70 |
| | | [Min; Max] | [1.6; 131.0] |

CV% = coefficient of variation (%)=sd/mean*100;
CV% geo-mean=(sqrt (exp (variance for log transformed data)-1))*100

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**Summary statistics of duration (in days) of B cell recovery from baseline (PD analysis set) – Part 2**

| | VAY736 0.6mg/kg N=6 | VAY736 2mg/kg N=6 |
|---|---|---|
| n | 6 | 6 |
| mean | 547 | 609 |
| SD | 198 | 371 |
| minimum | 262 | 135 |
| median | 507 | 562 |
| maximum | 783 | 1273 |

Criteria used: time to return to >= 80 cells/uL (for patients with >= 80 cells/uL at baseline) or at least 80% of baseline levels (for patients with < 80 cells/uL at baseline)
Due to a protocol amendment, the criteria used for patient 5209 was: time to return to >= 50 cells/uL (for patients with >= 50 cells/uL at baseline) or at least 80% of baseline levels (for patients with < 50 cells/uL at baseline)

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**Summary of B cell count data (PD analysis set) – Part 3**

| Treatment: VAY736 60mg | | | |
|---|---|---|---|
| **Visit** | **Scheduled timepoint** | | **B cells (cells/uL)** |
| BAS | | n | 11 |
| | | Mean (SD) | 156.19 (86.308) |
| | | CV% mean | 55.3 |
| | | Geo-mean | 135.33 |
| | | CV% geo-mean | 64.0 |
| | | Median | 138.00 |
| | | [Min; Max] | [45.5; 366.0] |
| D2 | 24 | n | 12 |
| | | Mean (SD) | 8.45 (6.144) |
| | | CV% mean | 72.7 |
| | | Geo-mean | 6.76 |
| | | CV% geo-mean | 79.2 |
| | | Median | 7.15 |
| | | [Min; Max] | [2.2; 21.4] |
| D4 | 72 | n | 12 |
| | | Mean (SD) | 11.17 (9.801) |
| | | CV% mean | 87.8 |
| | | Geo-mean | 8.28 |
| | | CV% geo-mean | 92.8 |
| | | Median | 7.90 |
| | | [Min; Max] | [3.0; 31.1] |
| D7 | | n | 11 |
| | | Mean (SD) | 11.10 (9.672) |

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| Treatment: VAY736 60mg | | | |
|---|---|---|---|
| **Visit** | **Scheduled timepoint** | | **B cells (cells/uL)** |
| | | CV% mean | 87.1 |
| | | Geo-mean | 7.38 |
| | | CV% geo-mean | 139.6 |
| | | Median | 9.40 |
| | | [Min; Max] | [1.4; 30.6] |
| D15 | | n | 11 |
| | | Mean (SD) | 4.25 (5.165) |
| | | CV% mean | 121.7 |
| | | Geo-mean | 2.41 |
| | | CV% geo-mean | 166.8 |
| | | Median | 2.80 |
| | | [Min; Max] | [0.4; 18.6] |
| EOS | | n | 9 |
| | | Mean (SD) | 6.88 (6.364) |
| | | CV% mean | 92.5 |
| | | Geo-mean | 4.56 |
| | | CV% geo-mean | 139.0 |
| | | Median | 4.40 |
| | | [Min; Max] | [0.6; 18.1] |

CV% = coefficient of variation (%)=sd/mean*100;
CV% geo-mean=(sqrt (exp (variance for log transformed data)-1))*100

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## Summary of Safety

## Safety Results

### Adverse Events (AEs) by Preferred term:

**Incidence of AEs by preferred term - n patients (percent) of patients ) (Safety analysis set) - Part 1**

| | Placebo N=10 n (%) | VAY736 0.0003 mg/kg N=3 n (%) | VAY736 0.001 mg/kg N=3 n (%) | VAY736 0.003 mg/kg N=3 n (%) | VAY736 0.01 mg/kg N=3 n (%) | VAY736 0.03 mg/kg N=3 n (%) | VAY736 0.1 mg/kg N=3 n (%) | VAY736 0.3 mg/kg N=3 n (%) | VAY736 1 mg/kg N=3 n (%) | VAY736 3 mg/kg N=3 n (%) | VAY736 10 mg/kg N=3 n (%) | Total N=41 n (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patients with AE(s) | 8 (80.0) | 2 (66.7) | 2 (66.7) | 3 (100.0) | 3 (75.0) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 36 (87.8) |
| **Preferred term** | | | | | | | | | | | | |
| Headache | 7 (70.0) | 1 (33.3) | 0 (0.0) | 2 (66.7) | 1 (25.0) | 3 (100.0) | 3 (100.0) | 1 (33.3) | 1 (33.3) | 2 (66.7) | 1 (33.3) | 22 (53.7) |
| Nasopharyngitis | 1 (10.0) | 1 (33.3) | 2 (66.7) | 2 (66.7) | 0 (0.0) | 1 (33.3) | 2 (66.7) | 1 (33.3) | 3 (100.0) | 1 (33.3) | 2 (66.7) | 16 (39.0) |
| Body temperature increased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 1 (25.0) | 0 (0.0) | 3 (100.0) | 3 (100.0) | 1 (33.3) | 2 (66.7) | 2 (66.7) | 13 (31.7) |
| Nausea | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (66.7) | 0 (0.0) | 1 (33.3) | 1 (33.3) | 2 (66.7) | 0 (0.0) | 1 (33.3) | 1 (33.3) | 8 (19.5) |
| Arthralgia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 1 (25.0) | 2 (66.7) | 1 (33.3) | 0 (0.0) | 1 (33.3) | 1 (33.3) | 0 (0.0) | 7 (17.1) |
| Blood pressure increased | 2 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 0 (0.0) | 2 (66.7) | 1 (33.3) | 1 (33.3) | 0 (0.0) | 7 (17.1) |
| Chills | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 2 (66.7) | 1 (33.3) | 0 (0.0) | 1 (33.3) | 2 (66.7) | 0 (0.0) | 7 (17.1) |
| Pyrexia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 3 (100.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 1 (33.3) | 6 (14.6) |
| Feeling cold | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 2 (66.7) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 5 (12.2) |
| Back pain | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 2 (66.7) | 0 (0.0) | 4 (9.8) |
| Paraesthesia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (66.7) | 0 (0.0) | 1 (33.3) | 1 (33.3) | 0 (0.0) | 4 (9.8) |
| Rheumatoid arthritis* | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 3 (100.0) | 4 (9.8) |
| Upper respiratory tract infection | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (66.7) | 0 (0.0) | 2 (66.7) | 4 (9.8) |
| Feeling hot | 1 (10.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 1 (33.3) | 3 (7.3) |
| Urinary tract infection | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (7.3) |

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| | Placebo N=10 n (%) | VAY736 0.0003 mg/kg N=3 n (%) | VAY736 0.001 mg/kg N=3 n (%) | VAY736 0.003 mg/kg N=3 n (%) | VAY736 0.01 mg/kg N=3 n (%) | VAY736 0.03 mg/kg N=3 n (%) | VAY736 0.1 mg/kg N=3 n (%) | VAY736 0.3 mg/kg N=3 n (%) | VAY736 1 mg/kg N=3 n (%) | VAY736 3 mg/kg N=3 n (%) | VAY736 10 mg/kg N=3 n (%) | Total N=41 n (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Abdominal pain | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.9) |
| Abdominal pain upper | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 2 (4.9) |
| Agitation | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 2 (4.9) |
| Musculoskeletal chest pain | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 2 (4.9) |
| Myalgia | 1 (10.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.9) |
| Neutrophil count decreased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.9) |
| Oropharyngeal pain | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 2 (4.9) |
| Sciatica | 1 (10.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.9) |
| Toothache | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.9) |
| Vertigo | 1 (10.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.9) |
| Vomiting | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.9) |

Arranged in descending order of frequency (in total group) and by preferred term
N = number of subjects studied, n = number of subjects with at least one AE in the category

*These refer to flare of rheumatoid arthritis

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**Incidence of AEs by preferred term within 24h of dosing – Part 1 (Safety analysis set)**

| | Placebo N=10 n (%) | VAY736 0.0003 mg/kg N=3 n (%) | VAY736 0.001 mg/kg N=3 n (%) | VAY736 0.003 mg/kg N=3 n (%) | VAY736 0.01 mg/kg N=4 n (%) | VAY736 0.03 mg/kg N=3 n (%) | VAY736 0.1 mg/kg N=3 n (%) | VAY736 0.3 mg/kg N=3 n (%) | VAY736 1 mg/kg N=3 n (%) | VAY736 3 mg/kg N=3 n (%) | VAY736 10 mg/kg N=3 n (%) | Total N=41 n (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Subjects with AE(s) | 5 (50.0) | 1 (33.3) | 1 (33.3) | 2 (66.7) | 1 (25.0) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 28 (68.3) |
| Preferred term | | | | | | | | | | | | |
| Headache | 4 (40.0) | 1 (33.3) | 0 (0.0) | 1 (33.3) | 1 (25.0) | 3 (100.0) | 2 (66.7) | 1 (33.3) | 1 (33.3) | 2 (66.7) | 1 (33.3) | 17 (41.5) |
| Body temperature increased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 1 (25.0) | 0 (0.0) | 3 (100.0) | 3 (100.0) | 1 (33.3) | 2 (66.7) | 2 (66.7) | 13 (31.7) |
| Chills | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 1 (33.3) | 1 (33.3) | 0 (0.0) | 1 (33.3) | 2 (66.7) | 0 (0.0) | 6 (14.6) |
| Pyrexia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 3 (100.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 1 (33.3) | 6 (14.6) |
| Feeling cold | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 2 (66.7) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 5 (12.2) |
| Nausea | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 1 (33.3) | 0 (0.0) | 1 (33.3) | 1 (33.3) | 5 (12.2) |
| Blood pressure increased | 1 (10.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (66.7) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 4 (9.8) |
| Arthralgia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 3 (7.3) |
| Feeling hot | 1 (10.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 1 (33.3) | 3 (7.3) |
| Agitation | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 2 (4.9) |
| Myalgia | 1 (10.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.9) |
| Vomiting | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.9) |
| Abdominal pain upper | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Catheter site pain | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 1 (2.4) |
| Dizziness | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 1 (2.4) |
| Dysgeusia | 1 (10.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Erythema | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Erythema of eyelid | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Hypertension | 1 (10.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Infusion related reaction | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Musculoskeletal chest pain | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 1 (2.4) |

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| | Placebo N=10 n (%) | VAY736 0.0003 mg/kg N=3 n (%) | VAY736 0.001 mg/kg N=3 n (%) | VAY736 0.003 mg/kg N=3 n (%) | VAY736 0.01 mg/kg N=4 n (%) | VAY736 0.03 mg/kg N=3 n (%) | VAY736 0.1 mg/kg N=3 n (%) | VAY736 0.3 mg/kg N=3 n (%) | VAY736 1 mg/kg N=3 n (%) | VAY736 3 mg/kg N=3 n (%) | VAY736 10 mg/kg N=3 n (%) | Total N=41 n (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nasopharyngitis | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Oral dysaesthesia | 1 (10.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Vertigo | 1 (10.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |

Arranged in descending order of frequency (in total group) and by preferred term
N = number of subjects studied, n = number of subjects with at least one AE in the category

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**Incidence of AEs by preferred term starting 24 hours after dosing – Part 1 (Safety analysis set)**

| | Placebo N=10 n (%) | VAY736 0.0003 mg/kg N=3 n (%) | VAY736 0.001 mg/kg N=3 n (%) | VAY736 0.003 mg/kg N=3 n (%) | VAY736 0.01 mg/kg N=4 n (%) | VAY736 0.03 mg/kg N=3 n (%) | VAY736 0.1 mg/kg N=3 n (%) | VAY736 0.3 mg/kg N=3 n (%) | VAY736 1 mg/kg N=3 n (%) | VAY736 3 mg/kg N=3 n (%) | VAY736 10 mg/kg N=3 n (%) | Total N=41 n (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Subjects with AE(s) | 6 (60.0) | 1 (33.3) | 2 (66.7) | 3 (100.0) | 3 (75.0) | 3 (100.0) | 3 (100.0) | 2 (66.7) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 32 (78.0) |
| Preferred term | | | | | | | | | | | | |
| Nasopharyngitis | 1 (10.0) | 1 (33.3) | 2 (66.7) | 2 (66.7) | 0 (0.0) | 1 (33.3) | 2 (66.7) | 1 (33.3) | 3 (100.0) | 1 (33.3) | 2 (66.7) | 16 (39.0) |
| Headache | 3 (30.0) | 0 (0.0) | 0 (0.0) | 2 (66.7) | 0 (0.0) | 1 (33.3) | 1 (33.3) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 8 (19.5) |
| Arthralgia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 1 (25.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 4 (9.8) |
| Back pain | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 2 (66.7) | 0 (0.0) | 4 (9.8) |
| Paraesthesia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (66.7) | 0 (0.0) | 1 (33.3) | 1 (33.3) | 0 (0.0) | 4 (9.8) |
| Rheumatoid arthritis* | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 3 (100.0) | 4 (9.8) |
| Upper respiratory tract infection | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (66.7) | 0 (0.0) | 2 (66.7) | 4 (9.8) |
| Blood pressure increased | 1 (10.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 3 (7.3) |
| Nausea | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (7.3) |
| Urinary tract infection | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (7.3) |
| Abdominal pain | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.9) |
| Neutrophil count decreased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.9) |
| Oropharyngeal pain | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 2 (4.9) |
| Sciatica | 1 (10.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.9) |
| Toothache | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.9) |
| Vertigo | 1 (10.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.9) |
| Abdominal pain upper | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 1 (2.4) |
| Benign breast neoplasm | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Bone contusion | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Bone pain | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 1 (2.4) |

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| | Placebo N=10 n (%) | VAY736 0.0003 mg/kg N=3 n (%) | VAY736 0.001 mg/kg N=3 n (%) | VAY736 0.003 mg/kg N=3 n (%) | VAY736 0.01 mg/kg N=4 n (%) | VAY736 0.03 mg/kg N=3 n (%) | VAY736 0.1 mg/kg N=3 n (%) | VAY736 0.3 mg/kg N=3 n (%) | VAY736 1 mg/kg N=3 n (%) | VAY736 3 mg/kg N=3 n (%) | VAY736 10 mg/kg N=3 n (%) | Total N=41 n (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| C-reactive protein increased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Calcium deficiency | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Chills | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Cough | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Dental caries | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Diarrhoea | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Dupuytren's contracture | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 1 (2.4) |
| Dyspnoea exertional | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Ear pain | 1 (10.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Erythema of eyelid | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Fatigue | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 1 (2.4) |
| Femur fracture | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Fungal skin infection | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Gastroenteritis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 1 (2.4) |
| Haematemesis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 1 (2.4) |
| Haematoma | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Herpes simplex | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Hordeolum | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Hyperparathyroidism | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Infusion related reaction | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Injection site inflammation | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Joint injury | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Leukocytosis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Leukopenia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Ligament rupture | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |

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| | Placebo N=10 n (%) | VAY736 0.0003 mg/kg N=3 n (%) | VAY736 0.001 mg/kg N=3 n (%) | VAY736 0.003 mg/kg N=3 n (%) | VAY736 0.01 mg/kg N=4 n (%) | VAY736 0.03 mg/kg N=3 n (%) | VAY736 0.1 mg/kg N=3 n (%) | VAY736 0.3 mg/kg N=3 n (%) | VAY736 1 mg/kg N=3 n (%) | VAY736 3 mg/kg N=3 n (%) | VAY736 10 mg/kg N=3 n (%) | Total N=41 n (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lipase increased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Muscle spasms | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Musculoskeletal chest pain | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Neutrophil count increased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Oral herpes | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Osteoarthritis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Ovarian cyst | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Parathyroid tumour benign | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Petechiae | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Renal failure | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Sinusitis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Tibia fracture | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Tinnitus | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Torticollis | 1 (10.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| Urogenital infection bacterial | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |
| White blood cell count decreased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.4) |

Arranged in descending order of frequency (in total group) and by preferred term
N = number of subjects studied, n = number of subjects with at least one AE in the category

*These refer to flare of rheumatoid arthritis

NOVARTIS

## Overall incidence of AEs - number of events and number of patients (Safety analysis set) - Part 1

| | Placebo N=10 nE, nS (%) | VAY736 0.0003 mg/kg N=3 nE, nS (%) | VAY736 0.001 mg/kg N=3 nE, nS (%) | VAY736 0.003 mg/kg N=3 nE, nS (%) | VAY736 0.01 mg/kg N=4 nE, nS (%) | VAY736 0.03 mg/kg N=3 nE, nS (%) | VAY736 0.1 mg/kg N=3 nE, nS (%) | VAY736 0.3 mg/kg N=3 nE, nS (%) | VAY736 1 mg/kg N=3 nE, nS (%) | VAY736 3 mg/kg N=3 nE, nS (%) | VAY736 10 mg/kg N=3 nE, nS (%) | Total N=41 nE, nS (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AEs, Subjects with AEs | 20, 8 (80.0) | 2, 2 (66.7) | 3, 2 (66.7) | 26, 3 (100.0) | 12, 3 (75.0) | 24, 3 (100.0) | 38, 3 (100.0) | 22, 3 (100.0) | 25, 3 (100.0) | 19, 3 (100.0) | 23, 3 (100.0) | 214, 36 (87.8) |
| AEs of Mild intensity | 15, 7 (70.0) | 2, 2 (66.7) | 3, 2 (66.7) | 21, 3 (100.0) | 3, 2 (50.0) | 16, 3 (100.0) | 25, 3 (100.0) | 17, 3 (100.0) | 16, 3 (100.0) | 18, 3 (100.0) | 15, 3 (100.0) | 151, 34 (82.9) |
| AEs of Moderate intensity | 4, 4 (40.0) | 0, 0 (0.0) | 0, 0 (0.0) | 5, 1 (33.3) | 7, 3 (75.0) | 6, 2 (66.7) | 12, 3 (100.0) | 5, 3 (100.0) | 9, 3 (100.0) | 1, 1 (33.3) | 7, 3 (100.0) | 56, 23 (56.1) |
| AEs of Severe intensity | 1, 1 (10.0) | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 2, 1 (25.0) | 2, 1 (33.3) | 1, 1 (33.3) | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 1, 1 (33.3) | 7, 5 (12.2) |
| Study drug-related AEs | 11, 6 (60.0) | 0, 0 (0.0) | 3, 2 (66.7) | 17, 3 (100.0) | 3, 2 (50.0) | 20, 3 (100.0) | 23, 3 (100.0) | 9, 3 (100.0) | 5, 3 (100.0) | 12, 3 (100.0) | 9, 3 (100.0) | 112, 31 (75.6) |
| Serious AEs | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 1, 1 (33.3) | 0, 0 (0.0) | 2, 1 (33.3) | 0, 0 (0.0) | 1, 1 (33.3) | 4, 3 (7.3) |
| AEs leading to discontinuation of study treatment | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) |
| Study-drug related AEs leading to discontinuation of study treatment | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) |

N = number of subjects studied
nE = number of AE events in the category
nS = number of subjects with at least one AE in the category
% is based on the number of subjects

NOVARTIS

**Incidence of AEs by preferred term - n (percent) of patients (Safety analysis set) - Part 2**

| | VAY736 0.6mg/kg N=6 n (%) | VAY736 2mg/kg N=6 n (%) | Total N=12 n (%) |
|---|---|---|---|
| Patients with AE(s) | 6 (100.0) | 6 (100.0) | 12 (100.0) |
| Preferred term | | | |
| Injection related reaction | 3 (50.0) | 5 (83.3) | 8 (66.7) |
| Headache | 4 (66.7) | 1 (16.7) | 5 (41.7) |
| Nasopharyngitis | 2 (33.3) | 2 (33.3) | 4 (33.3) |
| Rheumatoid arthritis* | 2 (33.3) | 1 (16.7) | 3 (25.0) |
| Blood creatinine increased | 1 (16.7) | 0 (0.0) | 1 (8.3) |
| Bursitis | 0 (0.0) | 1 (16.7) | 1 (8.3) |
| Decreased appetite | 0 (0.0) | 1 (16.7) | 1 (8.3) |
| Diarrhoea | 0 (0.0) | 1 (16.7) | 1 (8.3) |
| Dyspepsia | 1 (16.7) | 0 (0.0) | 1 (8.3) |
| Fracture malunion | 1 (16.7) | 0 (0.0) | 1 (8.3) |
| Gastrooesophageal reflux disease | 1 (16.7) | 0 (0.0) | 1 (8.3) |
| Haematochezia | 0 (0.0) | 1 (16.7) | 1 (8.3) |
| Haemorrhoids | 1 (16.7) | 0 (0.0) | 1 (8.3) |
| Hiatus hernia | 1 (16.7) | 0 (0.0) | 1 (8.3) |
| Hyperhidrosis | 0 (0.0) | 1 (16.7) | 1 (8.3) |
| Hyperkalaemia | 1 (16.7) | 0 (0.0) | 1 (8.3) |
| Injection site reaction | 0 (0.0) | 1 (16.7) | 1 (8.3) |
| Muscle tightness | 0 (0.0) | 1 (16.7) | 1 (8.3) |
| Musculoskeletal pain | 0 (0.0) | 1 (16.7) | 1 (8.3) |
| Pyrexia | 0 (0.0) | 1 (16.7) | 1 (8.3) |
| Rosacea | 0 (0.0) | 1 (16.7) | 1 (8.3) |

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| | VAY736 0.6mg/kg N=6 n (%) | VAY736 2mg/kg N=6 n (%) | Total N=12 n (%) |
|---|---|---|---|
| Sinusitis | 1 (16.7) | 0 (0.0) | 1 (8.3) |
| Soft tissue disorder | 0 (0.0) | 1 (16.7) | 1 (8.3) |
| Urinary tract infection | 1 (16.7) | 0 (0.0) | 1 (8.3) |

Arranged in descending order of frequency (in total group) and by preferred term
N = number of subjects studied, n = number of subjects with at least one AE in the category

*These refer to flare of rheumatoid arthritis

**Incidence of AEs by preferred term within 24h of dosing – Part 2 (Safety analysis set)**

| | VAY736 0.6mg/kg N=6 n (%) | VAY736 2mg/kg N=6 n (%) | Total N=12 n (%) |
|---|---|---|---|
| Subjects with AE(s) | 6 (100.0) | 6 (100.0) | 12 (100.0) |
| Preferred term | | | |
| Injection-related reaction | 3 (50.0) | 5 (83.3) | 8 (66.7) |
| Headache | 4 (66.7) | 1 (16.7) | 5 (41.7) |
| Decreased appetite | 0 (0.0) | 1 (16.7) | 1 (8.3) |

Arranged in descending order of frequency (in total group) and by preferred term

N = number of subjects studied, n = number of subjects with at least one AE in the category

**Incidence of AEs by preferred term starting 24 hours after dosing – Part 2 (Safety analysis set)**

| | VAY736 0.6mg/kg N=6 n (%) | VAY736 2mg/kg N=6 n (%) | Total N=12 n (%) |
|---|---|---|---|
| Subjects with AE(s) | 6 (100.0) | 5 (83.3) | 11 (91.7) |

NOVARTIS

| | VAY736 0.6mg/kg N=6 n (%) | VAY736 2mg/kg N=6 n (%) | Total N=12 n (%) |
|---|---|---|---|
| Preferred term | | | |
| Nasopharyngitis | 2 (33.3) | 2 (33.3) | 4 (33.3) |
| Rheumatoid arthritis* | 2 (33.3) | 1 (16.7) | 3 (25.0) |
| Blood creatinine increased | 1 (16.7) | 0 (0.0) | 1 (8.3) |
| Bursitis | 0 (0.0) | 1 (16.7) | 1 (8.3) |
| Decreased appetite | 0 (0.0) | 1 (16.7) | 1 (8.3) |
| Diarrhoea | 0 (0.0) | 1 (16.7) | 1 (8.3) |
| Fracture malunion | 1 (16.7) | 0 (0.0) | 1 (8.3) |
| Gastrooesophageal reflux disease | 1 (16.7) | 0 (0.0) | 1 (8.3) |
| Haematochezia | 0 (0.0) | 1 (16.7) | 1 (8.3) |
| Haemorrhoids | 1 (16.7) | 0 (0.0) | 1 (8.3) |
| Hiatus hernia | 1 (16.7) | 0 (0.0) | 1 (8.3) |
| Hyperhidrosis | 0 (0.0) | 1 (16.7) | 1 (8.3) |
| Hyperkalaemia | 1 (16.7) | 0 (0.0) | 1 (8.3) |
| Injection site reaction | 0 (0.0) | 1 (16.7) | 1 (8.3) |
| Muscle tightness | 0 (0.0) | 1 (16.7) | 1 (8.3) |
| Musculoskeletal pain | 0 (0.0) | 1 (16.7) | 1 (8.3) |
| Pyrexia | 0 (0.0) | 1 (16.7) | 1 (8.3) |
| Rosacea | 0 (0.0) | 1 (16.7) | 1 (8.3) |
| Sinusitis | 1 (16.7) | 0 (0.0) | 1 (8.3) |
| Soft tissue disorder | 0 (0.0) | 1 (16.7) | 1 (8.3) |
| Urinary tract infection | 1 (16.7) | 0 (0.0) | 1 (8.3) |

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| | VAY736 0.6mg/kg N=6 n (%) | VAY736 2mg/kg N=6 n (%) | Total N=12 n (%) |
|---|---|---|---|

Arranged in descending order of frequency (in total group) and by preferred term
N = number of subjects studied, n = number of subjects with at least one AE in the category

*These refer to flare of rheumatoid arthritis

**Overall incidence of AEs - number of events and number of patients (Safety analysis set) - Part 2**

| | **VAY736 0.6mg/kg N=6 nE, nS (%)** | **VAY736 2mg/kg N=6 nE, nS (%)** | **Total N=12 nE, nS (%)** |
|---|---|---|---|
| AEs, Subjects with AEs | 23, 6 (100.0) | 22, 6 (100.0) | 45, 12 (100.0) |
| AEs of Mild intensity | 6, 5 (83.3) | 10, 5 (83.3) | 16, 10 (83.3) |
| AEs of Moderate intensity | 14, 6 (100.0) | 11, 6 (100.0) | 25, 12 (100.0) |
| AEs of Severe intensity | 3, 2 (33.3) | 1, 1 (16.7) | 4, 3 (25.0) |
| Study drug-related AEs | 9, 6 (100.0) | 9, 6 (100.0) | 18, 12 (100.0) |
| Serious AEs | 2, 1 (16.7) | 2, 1 (16.7) | 4, 2 (16.7) |
| AEs leading to discontinuation of study treatment | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) |
| Study-drug related AEs leading to discontinuation of study treatment | 0, 0 (0.0) | 0, 0 (0.0) | 0, 0 (0.0) |

N = number of subjects studied
nE = number of AE events in the category
nS = number of subjects with at least one AE in the category
% is based on the number of subjects

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**Incidence of AEs by preferred term - n (percent) of patients (Safety analysis set) - Part 3**

| | VAY736 60mg<br>N=12<br>n (%) |
|---|---|
| Patients with AE(s) | 12 (100.0) |
| Preferred term | |
| Injection related reaction | 10 (83.3) |
| Nasopharyngitis | 6 (50.0) |
| Headache | 3 (25.0) |
| Injection site reaction | 3 (25.0) |
| Rhinitis | 3 (25.0) |
| Bronchitis | 2 (16.7) |
| Abdominal pain | 1 (8.3) |
| Acne | 1 (8.3) |
| Aphasia | 1 (8.3) |
| Arthralgia | 1 (8.3) |
| Body temperature increased | 1 (8.3) |
| Chills | 1 (8.3) |
| Cognitive disorder | 1 (8.3) |
| Cough | 1 (8.3) |
| Diverticulitis | 1 (8.3) |
| Epistaxis | 1 (8.3) |
| Hypoaesthesia | 1 (8.3) |
| Memory impairment | 1 (8.3) |
| Myalgia | 1 (8.3) |
| Neck pain | 1 (8.3) |
| Nuchal rigidity | 1 (8.3) |

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| | VAY736 60mg<br>N=12<br>n (%) |
|---|---|
| Oropharyngeal pain | 1 (8.3) |
| Paraesthesia | 1 (8.3) |
| Road traffic accident | 1 (8.3) |
| Sternal fracture | 1 (8.3) |
| Synovitis | 1 (8.3) |

Arranged in descending order of frequency (in total group) and by preferred term
N = number of subjects studied, n = number of subjects with at least one AE in the category

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**Incidence of AEs by preferred term within 24h of 1st dosing – Part 3 (Safety analysis set)**

| | VAY736 60mg<br>N=12<br>n (%) |
|---|---|
| Subjects with AE(s) | 12 (100.0) |
| Preferred term | |
| Injection-related reaction | 10 (83.3) |
| Headache | 3 (25.0) |

Arranged in descending order of frequency and by preferred term
N = number of subjects studied, n = number of subjects with at least one AE in the category

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**Overall incidence of AEs - number of events and number of patients (Safety analysis set) - Part 3**

| | VAY736 60mg N=12 nE, nS (%) |
|---|---|
| AEs, Subjects with AEs | 57, 12 (100.0) |
| AEs of Mild intensity | 31, 9 (75.0) |
| AEs of Moderate intensity | 26, 11 (91.7) |
| AEs of Severe intensity | 0, 0 (0.0) |
| Study drug-related AEs | 41, 12 (100.0) |
| Serious AEs | 0, 0 (0.0) |
| AEs leading to discontinuation of study treatment | 3, 1 (8.3) |
| Study-drug related AEs leading to discontinuation of study treatment | 0, 0 (0.0) |

N = number of subjects studied
nE = number of AE events in the category
nS = number of subjects with at least one AE in the category
% is based on the number of subjects

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## Serious Adverse Events and Deaths

There were no deaths in the study. Serious adverse events and discontinuations in each part are shown in the section above.

## Immunogenicity

### Positive Immunogenicity (ADA) results – Part 1

| Subject | Treatment | Visit | Study day | Anti-drug Antibodies (Yes/No) | Titer |
|---|---|---|---|---|---|
| 5114 | Placebo | D1 Pre-dose | 1 | Yes | 7.87 |
| | | D27 | 21 | Yes | 8.57 |
| | | EOS | 57 | Yes | 12.60 |
| 5122 | Placebo | D1 Pre-dose | 1 | Yes | 2.90 |
| | | EOS | 28 | Yes | 2.67 |
| 5113 | 0.003 mg/kg VAY736 | D1 Pre-dose | 1 | Yes | - |
| 5117 | 0.01 mg/kg VAY736 | D1 Pre-dose | 1 | Yes | 82 |
| | | D21 | 21 | 40 | 40 |
| | | EOS | 49 | 42 | 42 |

**Positive Immunogenicity (ADA) results – Part 2**

| Subject | Treatment | Visit | Study day | Anti-drug Antibodies (Yes/No) | Titer |
|---|---|---|---|---|---|
| 5211 | 2 mg/kg VAY736 | D1 Pre-dose | 1 | Yes | 100 |

No patients had positive ADA results in Part 3.

## Other Relevant Findings

N/A.

## Conclusion:

VAY736 was safe and generally well tolerated apart from mild-to-moderate infusion/injection-related reactions observed in most patients. Nasopharyngitis was the second most reported AE, with some suspected to be related to study treatment. Local injection site reactions that were self-limited occurred in several patients upon re-dosing of VAY736.

VAY736 induced a rapid and profound depletion of circulating B cells in humans, in contrast to the more gradual rate of depletion observed pre-clinically in VAY736-treated cynomolgus monkeys. The duration of B-cell recovery varied considerably among patients and did not appear dose-dependent above a threshold 0.1 mg/kg dose level. No malignancies, serious infections or infections with atypical pathogens occurred during this recovery period.

Neutropenia and hemolytic anemia observed in VAY736-treated cynomolgus monkeys were not replicated in this clinical study, supporting the conclusions from investigations that these pre-clinical effects were species-specific.

PK profiles were consistent with that of a typical mAb of the IgG1 type but with a shorter half-life. No treatment-related anti-VAY736 antibodies were detected.

**Date of Clinical Trial Report**

19 October 2018