# Clinical trial results:
# A Randomized, Double-Blind, Double-Dummy, Active-Comparator, Multicenter Study to Evaluate the Efficacy and Safety of Rituximab Versus MMF in Patients With Pemphigus Vulgaris

## Summary

| | |
|---|---|
| EudraCT number | 2014-000382-41 |
| Trial protocol | DE ES IT FR |
| Global end of trial date | |

### Results information

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 18 December 2019 |
| First version publication date | 18 December 2019 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | WA29330 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02383589 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124., Basel, Switzerland, CH-4070 |
| Public contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com |
| Scientific contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Interim |
| Date of interim/final analysis | 28 November 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 November 2018 |
| Global end of trial reached? | No |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the efficacy of rituximab compared with Mycophenolate Mofetil (MMF) in achieving sustained complete remission, evaluated by the Pemphigus Disease Area Index (PDAI), and assessed at Week 52 in subjects with moderate-to-severely active PV; to evaluate the safety of rituximab compared with MMF with a focus on adverse events and safety laboratory values.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form

Background therapy:

Subjects received 60-120 mg/day oral prednisone or equivalent (1.0-1.5 mg/kg/day) before entering the trial.

Evidence for comparator:

MMF is considered standard of care treatment for pemphigus vulgaris according to published expert treatment guidelines

| | |
|---|---|
| Actual start date of recruitment | 26 May 2015 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 12 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Argentina: 8 |
| Country: Number of subjects enrolled | Brazil: 5 |
| Country: Number of subjects enrolled | Canada: 9 |
| Country: Number of subjects enrolled | Germany: 11 |
| Country: Number of subjects enrolled | Spain: 5 |
| Country: Number of subjects enrolled | France: 14 |
| Country: Number of subjects enrolled | Israel: 16 |
| Country: Number of subjects enrolled | Italy: 11 |
| Country: Number of subjects enrolled | Turkey: 13 |
| Country: Number of subjects enrolled | United States: 43 |
| Worldwide total number of subjects | 135 |
| EEA total number of subjects | 41 |

Notes:

| Subjects enrolled per age group | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 117 |
| From 65 to 84 years | 18 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

In this international study, 135 subjects were enrolled at 49 academic centers throughout North America, Europe, the Middle East, and South America.

### Pre-assignment

Screening details:

Subjects must have had a confirmed diagnosis of PV within the previous 24 months (by skin or mucosal biopsy and immunohistochemistry) and evidence of moderate-to-severely active disease at screening.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Rituximab (RTX) |

Arm description:

Subjects received rituximab by IV infusion on Days 1 and 15 with repeat administration on Days 168 and 182 provided specific safety criteria had been met. Subjects also received MMF matching placebo orally twice daily (every 12 hours, Q12H) from Day 1 to Week 52

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | Mabthera |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

RTX (1000 mg) was administered by intravenous (IV) infusion on Day 1 and Day 15, with repeat RTX administration on Day 168 and Day 182, provided that specific safety criteria had been met.

| | |
|---|---|
| Investigational medicinal product name | MMF-matching Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

MMF-matching placebo was administered PO twice daily (Q12H).

| | |
|---|---|
| **Arm title** | Mycophenolate Mofetil (MMF) |

Arm description:

Subjects received Mycophenolate Mofetil (MMF) orally twice daily (every 12 hours, Q12H) from Day 1 to Week 52. Subjects also received rituximab matching placebo by intravenous (IV) infusion on Days 1 and 15 with repeat administration on Days 168 and 182 provided specific safety criteria had been met.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | RTX-matching Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

RTX-matching placebo was administered by IV infusion on Day 1 and Day 15, with repeat RTX administration on Day 168 and Day 182, provided that specific safety criteria had been met.

| | |
|---|---|
| Investigational medicinal product name | Mycophenolate mofetil |
| Investigational medicinal product code | |
| Other name | Cellcept |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

MMF (500 mg) was administered per os (PO) twice daily (every 12 hours [Q12H]), starting with a total dose of 1 g/day on Day 1, and increased to 2g/day in divided doses by Week 2

| **Number of subjects in period 1** | Rituximab (RTX) | Mycophenolate Mofetil (MMF) |
|---|---|---|
| Started | 67 | 68 |
| Completed | 66 | 58 |
| Not completed | 1 | 10 |
| Consent withdrawn by subject | - | 5 |
| Adverse Event | 1 | 3 |
| Non-compliance with study drug | - | 1 |
| Lost to follow-up | - | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Rituximab (RTX) |
| Reporting group description: | |
| Subjects received rituximab by IV infusion on Days 1 and 15 with repeat administration on Days 168 and 182 provided specific safety criteria had been met. Subjects also received MMF matching placebo orally twice daily (every 12 hours, Q12H) from Day 1 to Week 52 | |
| Reporting group title | Mycophenolate Mofetil (MMF) |
| Reporting group description: | |
| Subjects received Mycophenolate Mofetil (MMF) orally twice daily (every 12 hours, Q12H) from Day 1 to Week 52. Subjects also received rituximab matching placebo by intravenous (IV) infusion on Days 1 and 15 with repeat administration on Days 168 and 182 provided specific safety criteria had been met. | |

| Reporting group values | Rituximab (RTX) | Mycophenolate Mofetil (MMF) | Total |
|---|---|---|---|
| Number of subjects | 67 | 68 | 135 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 54 | 63 | 117 |
| From 65-84 years | 13 | 5 | 18 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 50.66 | 46.34 | |
| standard deviation | ± 12.98 | ± 13.08 | - |
| Sex: Female, Male<br>Units: Subjects | | | |
| Male | 32 | 30 | 62 |
| Female | 35 | 38 | 73 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Hispanic or Latino | 13 | 21 | 34 |
| Not Hispanic or Latino | 45 | 41 | 86 |
| Not Stated | 9 | 6 | 15 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 1 | 1 |
| Asian | 3 | 1 | 4 |
| Black or African American | 1 | 2 | 3 |
| White | 49 | 51 | 100 |
| Unknown | 14 | 13 | 27 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Rituximab (RTX) |

Reporting group description:

Subjects received rituximab by IV infusion on Days 1 and 15 with repeat administration on Days 168 and 182 provided specific safety criteria had been met. Subjects also received MMF matching placebo orally twice daily (every 12 hours, Q12H) from Day 1 to Week 52

| | |
|---|---|
| Reporting group title | Mycophenolate Mofetil (MMF) |

Reporting group description:

Subjects received Mycophenolate Mofetil (MMF) orally twice daily (every 12 hours, Q12H) from Day 1 to Week 52. Subjects also received rituximab matching placebo by intravenous (IV) infusion on Days 1 and 15 with repeat administration on Days 168 and 182 provided specific safety criteria had been met.

| | |
|---|---|
| Subject analysis set title | Intent-to-Treat (ITT) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

All randomized subjects who received any part of an infusion of study drug or oral administration of study drug were included in the intent-to-treat (ITT) population. Sensitivity analyses of the efficacy outcomes were performed using the ITT population. Subjects who prematurely withdrew from the study for any reason and for whom an assessment was not performed for whatever reason were still included in the ITT analysis.

| | |
|---|---|
| Subject analysis set title | Modified ITT |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

The modified intent-to-treat (mITT) population included subjects in the ITT population, excluding the 10 telemedicine (TM) subjects. This population was used in the analyses of efficacy outcomes.

| | |
|---|---|
| Subject analysis set title | Safety Population |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The safety population included all subjects who were randomized and received any part of an infusion of study drug or oral administration of study drug. Subjects who received the incorrect therapy from that assigned were summarized according to the therapy actually received. This population was used for the analyses of safety outcomes.

### Primary: Percentage of Subjects (Excluding Telemedicine [TM] Subjects) Who Achieved Sustained Complete Remission, Evaluated by the Pemphigus Disease Area Index (PDAI) Activity Score

| | |
|---|---|
| End point title | Percentage of Subjects (Excluding Telemedicine [TM] Subjects) Who Achieved Sustained Complete Remission, Evaluated by the Pemphigus Disease Area Index (PDAI) Activity Score |

End point description:

The modified intent-to-treat (mITT) population included subjects in the ITT population, excluding the 10 telemedicine (TM) subjects. This population was used in the analyses of efficacy outcomes.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

From Baseline up to 52 Weeks (up to clinical cut-off date (CCOD) of 28 November 2018)

| End point values | Rituximab (RTX) | Mycophenolate Mofetil (MMF) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 62[1] | 63[2] | | |
| Units: Percentage | | | | |
| number (not applicable) | | | | |
| Week 52 | 40.3 | 9.5 | | |

Notes:

[1] - Only subjects for whom data were collected are included in the analysis.

[2] - Only subjects for whom data were collected are included in the analysis.

### Statistical analyses

| Statistical analysis title | Superiority |
|---|---|
| Comparison groups | Rituximab (RTX) v Mycophenolate Mofetil (MMF) |
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [3] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in proportion |
| Point estimate | 30.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 14.7 |
| upper limit | 45.15 |

Notes:

[3] - The analysis was stratified by the stratification factors applied at randomization.

## Secondary: Cumulative Oral Corticosteroid Dose

| End point title | Cumulative Oral Corticosteroid Dose |
|---|---|

End point description:

The modified intent-to-treat (mITT) population included subjects in the ITT population, excluding the 10 telemedicine (TM) subjects. This population was used in the analyses of efficacy outcomes.

| End point type | Secondary |
|---|---|

End point timeframe:

From Baseline up to 52 Weeks (up to CCOD of 28 November 2018)

| End point values | Rituximab (RTX) | Mycophenolate Mofetil (MMF) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 62[4] | 63[5] | | |
| Units: milligram (mg) | | | | |
| median (inter-quartile range (Q1-Q3)) | 2775.00 (2146.88 to 3610.00) | 4005.00 (2662.50 to 5815.00) | | |

Notes:

[4] - Only subjects for whom data were collected are included in the analysis.

[5] - Only subjects for whom data were collected are included in the analysis.

### Statistical analyses

| Statistical analysis title | Superiority |
|---|---|
| Comparison groups | Rituximab (RTX) v Mycophenolate Mofetil (MMF) |
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0005 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Total Number of Protocol Defined Disease Flares

| End point title | Total Number of Protocol Defined Disease Flares |
|---|---|

End point description:

Disease flare is defined as appearance of three or more new lesions a month that do not heal spontaneously within 1 week, or by the extension of established lesions, in a subject who has achieved disease control. The modified intent-to-treat (mITT) population included subjects in the ITT population, excluding the 10 telemedicine (TM) subjects. This population was used in the analyses of efficacy outcomes.

| End point type | Secondary |
|---|---|

End point timeframe:

From Baseline up to 52 Weeks (up to CCOD of 28 November 2018)

| End point values | Rituximab (RTX) | Mycophenolate Mofetil (MMF) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 62[6] | 63[7] | | |
| Units: Number | | | | |
| Number of subjects with at least one flare | 5 | 26 | | |
| Number of flares | 6 | 44 | | |

Notes:

[6] - Only subjects for whom data were collected are included in the analysis.

[7] - Only subjects for whom data were collected are included in the analysis.

### Statistical analyses

| Statistical analysis title | Superiority |
|---|---|
| Comparison groups | Rituximab (RTX) v Mycophenolate Mofetil (MMF) |

| | |
|---|---|
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [8] |
| Method | Negative Binominal Regression |
| Parameter estimate | Adjusted Rate Ratio |
| Point estimate | 0.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.05 |
| upper limit | 0.29 |

Notes:

[8] - The model was adjusted for the following covariates in addition to log (each subject's duration in study) as an offset: treatment, region, duration of illness, baseline PDAI activity score, and baseline prednisone dose.

## Secondary: Time to Initial Sustained Complete Remission

| | |
|---|---|
| End point title | Time to Initial Sustained Complete Remission |

End point description:

The modified intent-to-treat (mITT) population included subjects in the ITT population, excluding the 10 telemedicine (TM) subjects. This population was used in the analyses of efficacy outcomes. Only subjects for whom data were collected are included in the analysis. The end point couldnot be analyzed due to the limited number of events. The median is not estimable due to limited number of events. 9999=not estimable

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

From Baseline up to 52 Weeks (up to CCOD of 28 November 2018)

| End point values | Rituximab (RTX) | Mycophenolate Mofetil (MMF) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 62 | 63 | | |
| Units: Weeks | | | | |
| median (confidence interval 95%) | 9999 (32.1 to 9999) | 9999 (9999 to 9999) | | |

## Statistical analyses

| Statistical analysis title | Superiority |
|---|---|
| Comparison groups | Rituximab (RTX) v Mycophenolate Mofetil (MMF) |
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0003 [9] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 4.83 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.97 |
| upper limit | 11.81 |

Notes:

[9] - P-value is from a stratified log-rank test used to test the time to first disease flare between the RTX and MMF treatment arms over the 52-week treatment period, adjusting for the stratification factors applied at randomization

## Secondary: Time to Protocol-Defined Disease Flare

| | |
|---|---|
| End point title | Time to Protocol-Defined Disease Flare |

End point description:

Disease flare is defined as the appearance of three or more new lesions a month that do not heal spontaneously within 1 week or by the extension of established lesions in a subject who has achieved disease control. The modified intent-to-treat (mITT) population included subjects in the ITT population, excluding the 10 telemedicine (TM) subjects. This population was used in the analyses of efficacy outcomes. The median is not estimable due to limited number of events. 9999=not estimable

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

From Baseline up to 52 Weeks (up to CCOD of 28 November 2018)

| End point values | Rituximab (RTX) | Mycophenolate Mofetil (MMF) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 62[10] | 63[11] | | |
| Units: Weeks | | | | |
| median (confidence interval 95%) | 9999 (9999 to 9999) | 9999 (36.9 to 9999) | | |

Notes:

[10] - Only subjects for whom data were collected are included in the analysis.

[11] - Only subjects for whom data were collected are included in the analysis.

### Statistical analyses

| Statistical analysis title | Superiority |
|---|---|
| Comparison groups | Rituximab (RTX) v Mycophenolate Mofetil (MMF) |
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [12] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.06 |
| upper limit | 0.39 |

Notes:

[12] - P-value is from a stratified log-rank test used to test the time to first disease flare between the RTX and MMF treatment arms over the 52-week treatment period, adjusting for the stratification factors applied at randomization

## Secondary: Change in Health-Related Quality of Life (HRQoL), as Measured by the Dermatology Life Quality Index (DLQI) Score

| End point title | Change in Health-Related Quality of Life (HRQoL), as Measured by the Dermatology Life Quality Index (DLQI) Score |
|---|---|

End point description:

The modified intent-to-treat (mITT) population included subjects in the ITT population, excluding the 10 telemedicine (TM) subjects. This population was used in the analyses of efficacy outcomes. Only subjects for whom data were collected are included in the analysis. The measure type represents Estimated Mean estimated from adjusted MMRM.

| End point type | Secondary |
|---|---|

End point timeframe:

From Baseline up to 52 Weeks (up to CCOD of 28 November 2018)

| **End point values** | Rituximab (RTX) | Mycophenolate Mofetil (MMF) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 62[13] | 63[14] | | |
| Units: Number | | | | |
| arithmetic mean (standard error) | | | | |
| Baseline | 10.14 (± 7.89) | 11.09 (± 8.52) | | |
| Week 52 | -8.874 (± 0.532) | -6.002 (± 0.662) | | |

Notes:

[13] - The number of subjects analyzed is 57 at Baseline and 45 at Week 52

[14] - The number of subjects analyzed is 58 at Baseline and 27 at Week 52

### Statistical analyses

| **Statistical analysis title** | Superiority |
|---|---|
| Comparison groups | Rituximab (RTX) v Mycophenolate Mofetil (MMF) |
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0012 [15] |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Difference in Estimated Means |
| Point estimate | -2.872 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.577 |
| upper limit | -1.167 |

Notes:

[15] - P-value is from Mixed Model Repeated Measures (MMRM) with unstructured covariance matrix, adjusting for treatment, region, duration of illness, baseline DLQI score, visit, and an interaction terms for visit × baseline DLQI score and visit × treatment

## Secondary: Percentage of Subjects With Adverse Events (AE), Serious Adverse

## Events (SAE), and Corticosteroid-Related Adverse Events

| End point title | Percentage of Subjects With Adverse Events (AE), Serious Adverse Events (SAE), and Corticosteroid-Related Adverse Events |
|---|---|

End point description:

An adverse event is any untoward medical occurrence in a participant to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment. A serious adverse event is an adverse event that results in death or is life-threatening or requires/prolongs hospitalization or results in persistent/significant disability/incapacity or congenital abnormality/birth defect. Adverse events of Grade 3 of higher are severe and life-threatening adverse events CS-related adverse events - causality as determined by the investigator.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline up to 52 Weeks (up to CCOD of 28 November 2018)

| End point values | Rituximab (RTX) | Mycophenolate Mofetil (MMF) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 67 | 68 | | |
| Units: Percentage | | | | |
| number (not applicable) | | | | |
| Subjects with AE | 85.1 | 88.2 | | |
| Subjects with SAE | 22.4 | 14.7 | | |
| Subjects with Corticosteroid (CS) - Related AE | 34.3 | 38.2 | | |
| Subjects with CS-Related AE of Grade 3 or higher | 1.5 | 7.4 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With Anti-Drug Antibodies (ADA)

| End point title | Percentage of Subjects With Anti-Drug Antibodies (ADA)[16] |
|---|---|

End point description:

Subjects with treatment-induced and treatment-enhanced anti-drug antibodies. The clinical relevance of anti-rituximab antibody formation in RITUXAN treated pemphigus vulgaris (PV) subjects is unclear. The safety population (all subjects who were randomized and received any part of an infusion of study drug), only subjects for whom data were collected are included in the analysis.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline up to 52 Weeks (up to CCOD of 28 November 2018)

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was provided only for those arms which were planned to be reported.

| End point values | Rituximab (RTX) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 63[17] | | | |
| Units: Percentage | | | | |
| number (not applicable) | 31.7 | | | |

Notes:

[17] - Only subjects for whom data were collected are included in the analysis.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects with Immunoglobulin (Ig) Levels Below Lower Limit of Normal (LLN)

| End point title | Percentage of Subjects with Immunoglobulin (Ig) Levels Below Lower Limit of Normal (LLN) |
|---|---|

End point description:

In the RITUXAN arm, low IgG levels were commonly observed and low IgM levels were very commonly observed; however, there was no evidence of an increased risk of serious infections after the development of low IgG or IgM. The safety population included all subjects who were randomized and received any part of an infusion of study drug or oral administration of study drug.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline; Weeks 16, 24, 40 and 52; (end of treatment: up to Week 52) (up to CCOD of 28 November 2018)

| End point values | Rituximab (RTX) | Mycophenolate Mofetil (MMF) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 67 | 68 | | |
| Units: Percentage | | | | |
| number (not applicable) | | | | |
| Baseline (IgA) | 0 | 0 | | |
| Week 16 (IgA) | 0 | 1.8 | | |
| Week 24 (IgA) | 1.7 | 2.2 | | |
| Week 40 (IgA) | 0 | 2.7 | | |
| Week 52 (IgA) | 0 | 3.6 | | |
| Baseline (IgG) | 6.1 | 6.0 | | |
| Week 16 (IgG) | 9.8 | 1.8 | | |
| Week 24 (IgG) | 3.4 | 2.2 | | |
| Week 40 (IgG) | 3.5 | 0 | | |
| Week 52 (IgG) | 4.3 | 0 | | |
| Baseline (IgM) | 7.6 | 11.9 | | |
| Week 16 (IgM) | 24.6 | 23.2 | | |
| Week 24 (IgM) | 27.1 | 28.3 | | |
| Week 40 (IgM) | 29.8 | 24.3 | | |
| Week 52 (IgM) | 29.8 | 28.6 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Baseline up to Week 52 (up to CCOD of 28 November 2018)

Adverse event reporting additional description:

The safety population included all subjects who were randomized and received any part of an infusion of study drug or oral administration of study drug. Subjects who received the incorrect therapy from that assigned were summarized according to the therapy actually received. This population was used for the analyses of safety outcomes.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Rituximab (RTX) |

Reporting group description:

Participants received rituximab by IV infusion on Days 1 and 15 with repeat administration on Days 168 and 182 provided specific safety criteria had been met. Participants also received MMF matching placebo orally Q12H from Day 1 to Week 52.

| | |
|---|---|
| Reporting group title | Mycophenolate Mofetil (MMF) |

Reporting group description:

Participants received Mycophenolate Mofetil (MMF) orally twice daily (every 12 hours, Q12H) from Day 1 to Week 52. Participants also received rituximab matching placebo by intravenous (IV) infusion on Days 1 and 15 with repeat administration on Days 168 and 182 provided specific safety criteria had been met.

| Serious adverse events | Rituximab (RTX) | Mycophenolate Mofetil (MMF) | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 15 / 67 (22.39%) | 10 / 68 (14.71%) | |
| number of deaths (all causes) | 0 | 1 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| SMALL CELL LUNG CANCER | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Injury, poisoning and procedural complications | | | |
| INFUSION RELATED REACTION | | | |
| subjects affected / exposed | 3 / 67 (4.48%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LUMBAR VERTEBRAL FRACTURE | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PELVIC FRACTURE | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| MYOCARDIAL INFARCTION | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| PARAESTHESIA | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HAEMATEMESIS | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ILEUS | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INCARCERATED UMBILICAL HERNIA | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders | | | |
| ACUTE PULMONARY OEDEMA | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHRONIC OBSTRUCTIVE PULMONARY DISEASE | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DYSPNOEA | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PULMONARY EMBOLISM | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 2 / 68 (2.94%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| SKIN ULCER | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| URINARY RETENTION | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| BURSITIS INFECTIVE | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CELLULITIS | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 67 (1.49%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HERPES ZOSTER | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFLUENZA | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONIA | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONIA VIRAL | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PYELONEPHRITIS | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PYELONEPHRITIS ACUTE | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SEPSIS | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SKIN INFECTION | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | Rituximab (RTX) | Mycophenolate Mofetil (MMF) | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 42 / 67 (62.69%) | 41 / 68 (60.29%) | |
| Injury, poisoning and procedural complications | | | |
| INFUSION RELATED REACTION | | | |
| subjects affected / exposed | 12 / 67 (17.91%) | 5 / 68 (7.35%) | |
| occurrences (all) | 19 | 6 | |
| Vascular disorders | | | |
| HYPERTENSION | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | 4 / 68 (5.88%) | |
| occurrences (all) | 2 | 4 | |
| Nervous system disorders | | | |
| DIZZINESS | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 2 / 68 (2.94%) | |
| occurrences (all) | 4 | 2 | |
| HEADACHE | | | |
| subjects affected / exposed | 10 / 67 (14.93%) | 6 / 68 (8.82%) | |
| occurrences (all) | 17 | 7 | |
| Blood and lymphatic system disorders | | | |
| LYMPHOPENIA | | | |
| subjects affected / exposed | 8 / 67 (11.94%) | 1 / 68 (1.47%) | |
| occurrences (all) | 14 | 1 | |
| General disorders and administration site conditions | | | |

| | | | |
|---|---|---|---|
| ASTHENIA | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 4 / 68 (5.88%) | |
| occurrences (all) | 5 | 4 | |
| FATIGUE | | | |
| subjects affected / exposed | 5 / 67 (7.46%) | 3 / 68 (4.41%) | |
| occurrences (all) | 8 | 3 | |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | 6 / 68 (8.82%) | |
| occurrences (all) | 2 | 8 | |
| Gastrointestinal disorders | | | |
| DIARRHOEA | | | |
| subjects affected / exposed | 3 / 67 (4.48%) | 10 / 68 (14.71%) | |
| occurrences (all) | 5 | 11 | |
| NAUSEA | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | 4 / 68 (5.88%) | |
| occurrences (all) | 4 | 4 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| COUGH | | | |
| subjects affected / exposed | 6 / 67 (8.96%) | 2 / 68 (2.94%) | |
| occurrences (all) | 6 | 2 | |
| OROPHARYNGEAL PAIN | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 3 / 68 (4.41%) | |
| occurrences (all) | 4 | 3 | |
| Skin and subcutaneous tissue disorders | | | |
| ALOPECIA | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | 5 / 68 (7.35%) | |
| occurrences (all) | 2 | 5 | |
| Psychiatric disorders | | | |
| INSOMNIA | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 6 / 68 (8.82%) | |
| occurrences (all) | 1 | 6 | |
| Musculoskeletal and connective tissue disorders | | | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 6 / 67 (8.96%) | 2 / 68 (2.94%) | |
| occurrences (all) | 6 | 2 | |
| BACK PAIN | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 6 / 67 (8.96%) | 1 / 68 (1.47%) | |
| occurrences (all) | 6 | 1 | |
| Infections and infestations | | | |
| NASOPHARYNGITIS | | | |
| subjects affected / exposed | 6 / 67 (8.96%) | 8 / 68 (11.76%) | |
| occurrences (all) | 8 | 12 | |
| ORAL CANDIDIASIS | | | |
| subjects affected / exposed | 6 / 67 (8.96%) | 6 / 68 (8.82%) | |
| occurrences (all) | 8 | 6 | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 6 / 67 (8.96%) | 5 / 68 (7.35%) | |
| occurrences (all) | 9 | 6 | |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 5 / 67 (7.46%) | 2 / 68 (2.94%) | |
| occurrences (all) | 6 | 2 | |
| Metabolism and nutrition disorders | | | |
| HYPOPHOSPHATAEMIA | | | |
| subjects affected / exposed | 5 / 67 (7.46%) | 0 / 68 (0.00%) | |
| occurrences (all) | 5 | 0 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 06 September 2014 | (1) It was clarified that certain additional safety criteria must have been met in order to resume either rituximab/placebo or MMF/placebo after treatment interruption, and to receive repeat rituximab/placebo infusions on Day 168 and Day 182. (2) The option to administer rituximab/placebo study drug at a faster infusion rate at Day 168 and Day 182 was removed. (3) Progression of PV, worsening, disease flare, or treatment failure was not to be recorded as an AE or SAE, and was to be captured as efficacy assessment data only. (4) The following sections were added: a section on dosage modification and treatment interruption, a section on the efficacy and safety of MMF in PV, and a section on side effects known to be associated with MMF. (5) Additional criteria for study treatment discontinuation were added, including severe allergic or anaphylactic study treatment-related reaction, NCI CTCAE Grade 4 (life-threatening) event during or within 24 hours of an infusion, and pure red cell aplasia. (6) Text was added to clarify the management of specific AEs, particularly infections and IRRs: - Infections: repeat infusions of rituximab (or matching placebo) were only to be considered after any infection had fully resolved. Additionally, it was clarified that infections should be treated according to the local standard of care instead of symptomatically; - IRRs: it was clarified that subjects who experienced a Grade 4 (life-threatening) event during an infusion were to have their infusion stopped, and that additional infusions should not be given. (7) It was clarified that prolonged peripheral blood B cell depletion was an expected outcome of rituximab treatment and was not to be considered a toxicity. (8) Instructions regarding the initial dose of prednisone or equivalent in the range of 1.0 to 1.5 mg/kg/day was updated to 60 to 120 mg/day from 80 to 120 mg/day. |
| 06 July 2015 | (1) The PDAI in Appendix 4 was replaced with a corrected version. In the previous version of the protocol (Version 2), the PDAI was reproduced with permission from Clinics of Dermatology (2012); however, in 2015, it was discovered that Clinics of Dermatology had published an erroneous version of the PDAI that omitted the column to evaluate the number of lesions if </=3 for disease activity. The erroneous version of the PDAI was replaced with the validated version, and the protocol was updated to reflect the correct information, including instructions on the scoring method. (2) During an iDMC organizational meeting on 7 Feb 2015, the iDMC advised the Sponsor to consider that clinical definitions of treatment failure may not be the same as the statistical definition of treatment failure (i.e., non-responder). Relevant section of the protocol was therefore amended, per the iDMC recommendation, to align the clinical definitions of treatment failure with "non-responder" classification for the primary analysis. To achieve this, one definition was amended and two definitions were deleted to avoid treatment bias and premature rescue. (3) The non-responder rule was updated to clarify the scenarios in which subjects will be imputed as non-responders. The previous wording referred to the non-responder categorization being applied at the time of withdrawal or treatment failure. This wording was potentially misleading given that the primary endpoint required a 16-week consecutive duration at any time during the 52-week treatment period. Therefore, additional wording was added for clarification purposes and did not deviate from the original intent. |

| | |
|---|---|
| 15 January 2016 | (1) A typographical error stating that urine and serum pregnancy tests were being performed at the sensitivity of 50 mIU/mL was corrected, as pregnancy tests were being performed at the recommended sensitivity of 25 mIU/mL. (2) It was clarified that female subjects who were not postmenopausal must have had two negative pregnancy test results prior to starting study treatment, with a specific time interval between the two pregnancy tests. The timing for the serum pregnancy test during the screening period was changed to clarify that the screening pregnancy test must have been performed 8 to 10 days before the baseline/Day 1 urine pregnancy test (i.e., between Day -8 and Day -10) instead of at Day -1 to Day -28. (3) Contraception requirements were updated to include male patients who had undergone a vasectomy and female partners of male subjects who received MMF. (4) Wording was included that male subjects should advise their female partners to use a highly effective method of contraception during the study and for 12 months after stopping treatment. (5) Footnote "o" in the schedule of assessments was changed to address a typographical error. In the previous version of the protocol (Version 3), the footnote specified that certain blood chemistry values were to be collected at Weeks 1, 15, 24, and 26; however, Week 15 was incorrect, and the timing was changed to Weeks 1, 2, 24, and 26. |
| 15 January 2016 | (6) It was clarified that, before Week 12, patients who experienced treatment failure required an early withdrawal visit and were to be followed in the SFU period to receive standard-of-care treatment. (7) The inclusion criterion regarding first confirmed diagnosis of PV within the previous 24 months based on histological features of acantholysis via skin or mucosal biopsy was revised to include additional acceptable confirmatory tests for PV diagnosis besides tissue-bound IgG antibodies by direct immunofluorescence on the surface of affected epithelium. The diagnosis of PV was based on histological features of acantholysis via skin or mucosal biopsy and one of the following: tissue-bound IgG antibodies by direct immunofluorescence on the surface of affected epithelium or serological detection of serum Dsg3 autoantibodies against epithelial cell surface either by indirect immunofluorescence microscopy or by enzyme-linked immunosorbent assay. (8) It was clarified that the iDMC would review the safety data of TM subjects. |
| 19 December 2017 | The protocol was amended to address FDA's recommendation that data obtained from TM subjects was considered to be exploratory in nature and therefore the primary analysis for establishing efficacy was to be based on the ITT population for subjects who were not recruited via TM. The following changes were made to the protocol to address this recommendation, as follows: (1) An additional minimum of 8 non-TM subjects was to be recruited into this study to maintain sufficient statistical power for the primary analysis, thereby increasing the overall enrollment from approximately 124 to approximately 132 subjects with PV. (2) The Statistical Considerations section was updated, stipulating that all efficacy outcomes would be analyzed using the mITT population and excluding subjects who were enrolled via TM. (3) he primary efficacy outcome measure was revised to reflect the exclusion of TM subjects. (4) A new primary analysis population was added, the mITT population, which included subjects in the ITT population, excluding the 10 subjects enrolled via TM. This population was to be used in the analyses of efficacy outcomes. (5) The analysis population to be used for the secondary efficacy endpoints was changed to the mITT population. (6) Exploratory analyses were updated to include a statement on descriptive statistics for evaluation of the 10 subjects recruited via TM. (7) In addition, the following change has been made: An exploratory objective and exploratory outcome measure to evaluate the proportion of subjects experiencing treatment failure in each treatment arm were added. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported