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 Units: Subjects			
Adults (18-64 years)	54	63	117
From 65-84 years	13	5	18
Age Continuous Units: Years			
arithmetic mean	50.66	46.34	
standard deviation	± 12.98	± 13.08	-
Sex: Female, Male Units: Subjects			
Male	32	30	62
Female	35	38	73
Race/Ethnicity, Customized Units: Subjects			

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%)	
		0 / 1	

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