



Clinical trial results:

A Randomized, Double Blind, Placebo Controlled, Parallel Group Study to Investigate the Efficacy and Safety of Ofatumumab Injection for Subcutaneous Use in Subjects with Pemphigus Vulgaris

Summary

EudraCT number	2013-001370-20
Trial protocol	IT HR GR PL
Global end of trial date	11 January 2018

Results information

Result version number	v1 (current)
This version publication date	25 January 2019
First version publication date	06 February 2019

Trial information

Trial identification

Sponsor protocol code	COMB157J2301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01920477
WHO universal trial number (UTN)	-
Other trial identifiers	OPV116910: GSK1841157

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 011 888-669-6682, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 011 888-669-6682, Novartis.email@novartis.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	Final
Date of interim/final analysis	11 January 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 January 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine the efficacy, based on disease remission, of ofatumumab SC at a dose of 20 mg administered every 4 weeks (with an additional 20 mg loading dose (ie, 40 mg total) at both Week 0 and Week 4) in subjects with PV.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 August 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Japan: 2
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	35
EEA total number of subjects	12

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)	34
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Sixty-nine subjects were screened.

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
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Arm title	Ofatumumab
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Arm description:

Subject will receive subcutaneous administration of ofatumumab 20 mg once every 4 weeks through Week 56, with an additional 20 mg dose (that is 40mg total) at both Week 0 and Week 4.

Arm type	Experimental
Investigational medicinal product name	ofatumumab
Investigational medicinal product code	
Other name	OMB157
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Ofatumumab was administered once every 4 weeks for a total of 56 weeks (total of 17 injections across 15 monthly dosing visits). Subjects received two loading doses of 20 mg SC injections (40 mg total) at the Baseline (Week 0) and Week 4 visits.

Arm title	Placebo
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Arm description:

Subject will receive subcutaneous administration of matching placebo of ofatumumab once every 4 weeks through Week 56, with an additional dose at both Week 0 and Week 4.

Arm type	Placebo
Investigational medicinal product name	matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Matching placebo was administered once every 4 weeks for a total of 56 weeks (total of 17 injections across 15 monthly dosing visits). Subjects received two loading doses of 20 mg SC injections (40 mg total) of matching placebo at the Baseline (Week 0) and Week 4 visits.

Number of subjects in period 1	Ofatumumab	Placebo
Started	17	18
Required Individualized Follow-up	1 ^[1]	0 ^[2]
Completed	2	1
Not completed	15	17
Study closed/terminated	14	15
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	1
Lack of efficacy	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One patient entered an individualized patient follow up per the protocol

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One patient entered an individualized patient follow up per the protocol

Baseline characteristics

Reporting groups

Reporting group title	Ofatumumab
Reporting group description:	
Subject will receive subcutaneous administration of ofatumumab 20 mg once every 4 weeks through Week 56, with an additional 20 mg dose (that is 40mg total) at both Week 0 and Week 4.	
Reporting group title	Placebo
Reporting group description:	
Subject will receive subcutaneous administration of matching placebo of ofatumumab once every 4 weeks through Week 56, with an additional dose at both Week 0 and Week 4.	

Reporting group values	Ofatumumab	Placebo	Total
Number of subjects	17	18	35
Age categorical			
Units: Subjects			
Adults (18-64 years)	17	17	34
From 65-84 years	0	1	1
Age Continuous			
Units: years			
arithmetic mean	49.6	47.1	
standard deviation	± 8.70	± 11.20	-
Sex: Female, Male			
Units: Subjects			
Female	10	8	18
Male	7	10	17
Race/Ethnicity, Customized			
Units: Subjects			
African American/African Heritage	1	0	1
American Indian or Alaskan Native	1	2	3
Asian - East Asian Heritage	2	0	2
Asian - Japanese Heritage	1	1	2
White - Arabic/North African Heritage	2	1	3
White - White/ Caucasian/ European Heritage	10	14	24

End points

End points reporting groups

Reporting group title	Ofatumumab
Reporting group description:	
Subject will receive subcutaneous administration of ofatumumab 20 mg once every 4 weeks through Week 56, with an additional 20 mg dose (that is 40mg total) at both Week 0 and Week 4.	
Reporting group title	Placebo
Reporting group description:	
Subject will receive subcutaneous administration of matching placebo of ofatumumab once every 4 weeks through Week 56, with an additional dose at both Week 0 and Week 4.	

Primary: Number of subjects who experienced sustained remission on minimal steroid therapy

End point title	Number of subjects who experienced sustained remission on minimal steroid therapy ^[1]
End point description:	
Time from randomization to the time of the subject's initial reduction of prednisone/prednisolone dose to ≤ 10 mg/day and maintained a dose ≤ 10 mg/day with no new or nonhealing lesions for ≥ 8 weeks and maintained the status until Week 60 was assessed. No participants met the criteria so no analysis was performed	
End point type	Primary
End point timeframe:	
Baseline up to approximately 60 weeks	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.	
Justification: No analysis was completed because no patients experienced sustained remission	

End point values	Ofatumumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Duration of remission on minimal steroid therapy

End point title	Duration of remission on minimal steroid therapy ^[2]
End point description:	
Sum of all periods of absence of new or nonhealing lesions while on an oral prednisone/prednisolone dose of ≤ 10 mg/day up to Week 60 was assessed.	
End point type	Primary
End point timeframe:	
Baseline up to approximately 60 weeks	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No analysis was completed

End point values	Ofatumumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: days				
arithmetic mean (standard deviation)	168.0 (± 73.33)	122.0 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving remission on minimal steroid therapy at Week 60

End point title	Percentage of subjects achieving remission on minimal steroid therapy at Week 60
End point description:	Percentage of subjects who achieved absence of new or nonhealing lesions while on an oral prednisone/prednisolone dose of ≤10 mg/day for > or = 8 weeks at Week 60 was assessed. Percentages were rounded up. Time to remission was not estimable.
End point type	Secondary
End point timeframe:	
Week 60	

End point values	Ofatumumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: percentage of participants	18	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to remission while on minimal steroid therapy by Week 60.

End point title	Time to remission while on minimal steroid therapy by Week 60.
End point description:	Time from randomization to the time of the subject's initial reduction of prednisone/prednisolone dose to ≤10 mg/day and maintained dose at ≤10 mg/day with no new or nonhealing lesions for ≥8 weeks by Week 60 was assessed
End point type	Secondary

End point timeframe:

Baseline up to approximately 60 weeks

End point values	Ofatumumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: days				
median (confidence interval 95%)	99999 (57.0 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving remission while off steroid therapy by Week 60

End point title	Percentage of subjects achieving remission while off steroid therapy by Week 60
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End point description:

Percentage of subjects with initial reduction of all steroids for ≥ 8 weeks with an absence of new or nonhealing (established) lesions by Week 60 were to be assessed. All subjects remained on prednisone/prednisolone so this endpoint could not be analyzed. Time to remission off steroid therapy also could not be analyzed

End point type	Secondary
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End point timeframe:

Baseline up to approximately 60 weeks

End point values	Ofatumumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: percentage of participants	99999	99999		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days a subject maintained minimal steroid therapy by Week 60.

End point title	Number of days a subject maintained minimal steroid therapy by Week 60.
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End point description:

Number of days a subject maintained minimal steroid therapy (an oral prednisone/prednisolone dose of ≤ 10 mg/day in the absence of new or nonhealing lesions) by Week 60.

End point type	Secondary
End point timeframe:	
Baseline up to approximately 60 weeks	

End point values	Ofatumumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: days				
arithmetic mean (standard deviation)	168 ($\pm$ 73.33)	122.0 ($\pm$ 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to initial flare/relapse by Week 60

End point title	Time to initial flare/relapse by Week 60
End point description:	
Time from randomization to the time of appearance of ≥ 3 new lesions within 1 month that did not heal spontaneously within 1 week, or to the time when there was an extension of lesions that were present at the randomization by Week 60 was assessed. Confidence Intervals for Ofatumumab are not valid values. System limitations do not allow NE for not estimable	
End point type	Secondary
End point timeframe:	
Baseline up to approximately 60 weeks	

End point values	Ofatumumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: days				
median (confidence interval 95%)	448 (99 to 99999)	169.0 (86.0 to 284.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with no flare/relapse by Week 60. Values were rounded

End point title	Percentage of participants with no flare/relapse by Week 60. Values were rounded
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End point description:

Percentage of participants achieving absence of new or nonhealing lesions while on an oral prednisone/prednisolone dose of ≤ 10 mg/day and did not subsequently have a appearance of ≥ 3 new lesions within 1 month that did not heal spontaneously within 1 week, or to the time when there was an extension of lesions that were present at the randomization by Week 60 was assessed. Percentages were rounded because of system limitation of not allowing a decimal

End point type	Secondary
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End point timeframe:

Baseline up to approximately 60 weeks

End point values	Ofatumumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: percentage of participants				
Week 2 no flare n=17,17	100	94		
Week 2 no new/nonhealing lesions n=17,17	47	22		
Week 4 no flare n=15,16	88	83		
Week 4 no new/nonhealing lesions n=15,16	47	39		
Week 6 no flare n=12,15	71	78		
Week 6 no new/nonhealing lesions n=12,15	41	33		
Week 8 no flare n=11,14	65	72		
Week 8 no new/nonhealing lesions n=11,14	35	33		
Week 12 no flare n=10,12	59	56		
Week 12 no new/nonhealing lesions n=10,12	35	17		
Week 16 no flare n=9,12	53	61		
Week 16 no new/nonhealing lesions n=9,12	26	17		
Week 20 no flare n=8,12	47	50		
Week 20 no new/nonhealing lesions n=8,12	29	17		
Week 24 no flare n=8,11	47	39		
Week 24 no new/nonhealing lesions n=8,11	35	17		
Week 28 no flare n=5,7	29	22		
Week 28 no new/nonhealing lesions n=5,7	18	11		
Week 32 no flare n=6,6	35	28		
Week 32 no new/nonhealing lesions n=6,6	18	6		
Week 36 no flare n=4,3	24	11		
Week 36 no new/nonhealing lesions n=4,3	6	6		
Week 40 no flare n=3,2	18	6		
Week 40 no new/nonhealing lesions n=	12	0		
Week 44 no flare n=3,2	18	6		
Week 44 no new/nonhealing lesions n=3,2	6	0		
Week 48 no flare n=3,1	18	0		

Week 48 no new/nonhealing lesions n=3,1	0	0		
Week 52 no flare n=2,1	12	6		
Week 52 no new/nonhealing lesions n=2,1	12	0		
Week 56 no flare n=2,1	12	0		
Week 56 no new/nonhealing lesions n=2,1	6	0		
Week 60 no flare n=17,17	88	83		
Week 60 no new/nonhealing lesions n=17,17	53	33		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma trough concentrations of population pharmacokinetics (PK) of ofatumumab

End point title	Plasma trough concentrations of population pharmacokinetics (PK) of ofatumumab ^[3]
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End point description:

Plasma (trough) concentrations of ofatumumab, Exposure-response relationship, PK parameters include: Maximum concentration (C_{max}); time to maximum concentration (t_{max}); and area under the time-concentration curve (AUC).

End point type	Secondary
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End point timeframe:

Baseline up to approximately 60 weeks

Notes:

[3] - 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: No analysis was completed

End point values	Ofatumumab			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: ng/mL				
arithmetic mean (standard deviation)				
4 hours post dose SS n=1	56.60 (± 99999)			
Day 1 Steady State (SS) n=1	1917.50 (± 99999)			
Day 2 Steady State (SS) n=1	2994.20 (± 99999)			
Day 3 Steady State (SS) n=1	3553.80 (± 99999)			
Day 4 Steady State (SS) n=1	3619.20 (± 99999)			
Day 7 Steady State (SS) n=1	3434.90 (± 99999)			
Day 14 Steady State (SS) n=1	2055.30 (± 99999)			
Week 4 n=12	311.59 (± 278.011)			
Week 4 SS n=1	1132.70 (± 99999)			

Week 8 n=9	1253.60 ($\pm$ 439.574)			
Week 8 SS n=2	1456.95 ($\pm$ 668.994)			
Week 12 n=7	727.01 ($\pm$ 430.834)			
Week 12 SS n=3	900.00 ($\pm$ 455.930)			
Week 16 n=8	512.88 ($\pm$ 377.189)			
Week 16 SS n=1	1043.40 ($\pm$ 99999)			
Week 20 n=6	415.88 ($\pm$ 303.307)			
Week 20 SS n=2	720.10 ($\pm$ 246.356)			
Week 24 n=5	461.72 ($\pm$ 437.717)			
Week 24 SS n=3	686.10 ($\pm$ 329.699)			
Week 36 n=3	477.63 ($\pm$ 378.112)			
Week 36 SS n=1	931.20 ($\pm$ 99999)			
Week 48 n=2	352.95 ($\pm$ 300.591)			
Week 48 SS n=1	1230.40 ($\pm$ 99999)			
Week 52 SS n=1	897.30 ($\pm$ 99999)			
Week 56 n=2	436.40 ($\pm$ 511.662)			
Week 60 n=2	76.40 ($\pm$ 32.244)			
Early withdrawal n=12	925.91 ($\pm$ 971.715)			

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity of ofatumumab - Immunoglobulin A - values below lower limit of normal

End point title	Immunogenicity of ofatumumab - Immunoglobulin A - values below lower limit of normal
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End point description:

Immunogenicity will be assessed by the incidence, titer, and type of human anti-human antibody (HAHA) immune response

End point type	Secondary
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End point timeframe:

Baseline up to approximately 60 weeks

End point values	Ofatumumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: g/L				
Baseline n=17,18	1	0		
Week 12 n=10,11	1	0		
Week 16 n=0,1	0	0		
Week 24 n=8,11	1	0		
Week 36 n=4,3	1	0		
Week 48 n=3,1	1	0		
Week 52 n=2,1	1	0		
Week 56 n=2,1	1	0		
Week 60/Early withdrawal n=17,18	0	0		
First 12 weeks of therapy n=17,18	1	0		
During on therapy period n=17,18	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity of ofatumumab - Immunoglobulin G - values below lower limit of normal

End point title	Immunogenicity of ofatumumab - Immunoglobulin G - values below lower limit of normal
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End point description:

Immunogenicity will be assessed by the incidence, titer, and type of human anti-human antibody (HAHA) immune response

End point type	Secondary
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End point timeframe:

Baseline up to approximately 60 weeks

End point values	Ofatumumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: g/L				
Baseline n=17,18	1	2		
Week 12 n=10,11	0	1		
Week 16 n=0,1	0	1		
Week 24 n=8,11	0	1		
Week 36 n=4,3	0	0		
Week 48 n=3,1	0	0		
Week 52 n=2,1	0	0		
Week 56 n=2,1	0	0		
Week 60/Early withdrawal n=17,18	0	2		
First 12 weeks of therapy n=17,18	1	3		
During on therapy period n=17,18	1	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity of ofatumumab - Immunoglobulin M - values below lower limit of normal

End point title	Immunogenicity of ofatumumab - Immunoglobulin M - values below lower limit of normal
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End point description:

Immunogenicity will be assessed by the incidence, titer, and type of human anti-human antibody (HAHA) immune response

End point type	Secondary
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End point timeframe:

Baseline up to approximately 60 weeks

End point values	Ofatumumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: g/L				
Baseline n=17,18	1	1		
Week 12 n=10,11	4	1		
Week 24 n=8,11	4	0		
Week 36 n=4,3	4	0		
Week 48 n=3,1	3	0		
Week 52 n=2,1	2	0		
Week 56 n=2,1	2	0		
Week 60/Early withdrawal n=17,18	6	2		
First 12 weeks of therapy n=17,18	4	1		
During on therapy period n=17,18	6	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity of ofatumumab - largest decrease from baseline

End point title	Immunogenicity of ofatumumab - largest decrease from baseline
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End point description:

Immunogenicity will be assessed by the incidence, titer, and type of human anti-human antibody (HAHA) immune response

End point type	Secondary
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End point timeframe:

Baseline up to approximately 60 weeks

End point values	Ofatumumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: g/L				
arithmetic mean (standard deviation)				
Immunoglobulin A n=13,11	-0.185 (± 0.1181)	-0.472 (± 0.7116)		
Immunoglobulin G n=11,13	-1.172 (± 0.9390)	-0.955 (± 0.6205)		
Immunoglobulin M n=17,11	-0.231 (± 0.1152)	-0.263 (± 0.3053)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline for CD19+ B cell count

End point title	Change from Baseline for CD19+ B cell count
End point description: CD19+ B cell count will be performed using Flow Cytometry. Week 16 data values were not estimable therefore were not presented. System limitations do not allow NE (not estimable) for standard deviation, substituted values of 99999 are not valid data values	
End point type	Secondary
End point timeframe: Baseline up to approximately 60 weeks	

End point values	Ofatumumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: 10 ⁹ /L				
arithmetic mean (standard deviation)				
Week 12 n=10,10	-0.24940 (± 0.228704)	0.03080 (± 0.072358)		
Week 24 n=7,9	-0.28607 (± 0.265327)	-0.04022 (± 0.197867)		
Week 36 n=4,3	-0.20525 (± 0.052703)	-0.10033 (± 0.021385)		
Week 48 n=3,1	-0.19717 (± 0.061436)	-0.00200 (± 99999)		
Week 52 n=2,1	-0.16300 (± 0.023335)	0.09600 (± 99999)		
Week 56 n=2,1	-0.16300 (± 0.023335)	0.01000 (± 99999)		

Week 60/Early withdrawal n=17,18	-0.21403 ($\pm$ 0.190282)	0.00367 ($\pm$ 0.190375)		
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Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit up to approximately 60 weeks

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Ofatumumab SC
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Reporting group description:

Ofatumumab SC

Reporting group title	Placebo
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Reporting group description:

Placebo

Serious adverse events	Ofatumumab SC	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 17 (5.88%)	1 / 18 (5.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ofatumumab SC	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 17 (82.35%)	8 / 18 (44.44%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	2 / 17 (11.76%)	1 / 18 (5.56%)	
occurrences (all)	2	1	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	3 / 17 (17.65%)	0 / 18 (0.00%)	
occurrences (all)	3	0	
Fatigue			
subjects affected / exposed	2 / 17 (11.76%)	1 / 18 (5.56%)	
occurrences (all)	2	2	
Influenza like illness			
subjects affected / exposed	1 / 17 (5.88%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Local reaction			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	0 / 17 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	3 / 17 (17.65%)	0 / 18 (0.00%)	
occurrences (all)	5	0	

Reproductive system and breast disorders Semen discolouration subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Sinus congestion subjects affected / exposed occurrences (all) Upper respiratory tract congestion subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2 0 / 17 (0.00%) 0 1 / 17 (5.88%) 1 0 / 17 (0.00%) 0	0 / 18 (0.00%) 0 1 / 18 (5.56%) 1 0 / 18 (0.00%) 0 1 / 18 (5.56%) 1	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Persistent depressive disorder subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1 1 / 17 (5.88%) 1	1 / 18 (5.56%) 1 0 / 18 (0.00%) 0	
Investigations B-lymphocyte count decreased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Injury, poisoning and procedural complications Arthropod sting subjects affected / exposed occurrences (all) Post procedural complication subjects affected / exposed occurrences (all) Procedural nausea	1 / 17 (5.88%) 1 1 / 17 (5.88%) 1	0 / 18 (0.00%) 0 0 / 18 (0.00%) 0	

subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Procedural pain subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	1 / 18 (5.56%) 3	
Headache subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2	0 / 18 (0.00%) 0	
Syncope subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Tremor subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	1 / 18 (5.56%) 1	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Eye disorders Conjunctival discolouration subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Eye irritation subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Eye swelling subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Ocular hyperaemia			

subjects affected / exposed	1 / 17 (5.88%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Vision blurred			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	3 / 17 (17.65%)	1 / 18 (5.56%)	
occurrences (all)	3	1	
Tongue ulceration			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Dermatitis allergic			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	1 / 17 (5.88%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Rash			

subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	2 / 18 (11.11%) 2	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Nephrolithiasis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Nocturia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 17 (11.76%)	1 / 18 (5.56%)	
occurrences (all)	2	1	
Metatarsalgia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Muscular weakness			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Musculoskeletal discomfort			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Plantar fasciitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Cellulitis			

subjects affected / exposed	0 / 17 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Folliculitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Gastroenteritis viral			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Herpes simplex			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Oral candidiasis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 17 (11.76%)	1 / 18 (5.56%)	
occurrences (all)	3	2	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Hypoglycaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 June 2013	• The definition of 'remission' was clarified such that subjects with existing, healing lesions could be considered in remission if other criteria were met. • It was clarified that all subjects, including early withdrawals from treatment, were to be transitioned to the Individualized Follow-up Period. • Exclusion criterion 4 was modified to include subjects with prior systemic antibiotic pemphigus treatments as treatment effects on pemphigus lesions are minimal but subjects with prior methotrexate treatment within 8 weeks of entry were excluded as were subjects with prior total body irradiation, bone marrow transplantation, or anti-CD4 at any time. • Exclusion criterion 6 was modified to remove the prior treatment with any lymphocyte depleting therapies information which was more appropriately included within the prohibited medications and non-drug therapies section. • Exclusion criteria 11 was modified to exclude subjects with a potential risk factor for adverse cardiac outcomes based on screening ECG.
26 September 2013	• The pharmacodynamics objective was clarified as a population pharmacodynamics objective. • New PK endpoints, of plasma (trough) concentrations of ofatumumab and exposure response relationship, were added to determine ofatumumab plasma concentrations across the whole study population. Exclusion 9 was amended to include subjects with isolated predominantly indirect hyperbilirubinemia or CD4 count < 500cells/mm3
13 March 2014	• The dose and dosing interval were changed from 60 mg every 12 weeks to 20 mg every 4 weeks with an additional 20 mg loading dose at both Week 0 and Week 4. Dose rationale details were updated with data and pharmacometric modelling to support the change, details of the supplied study treatment were updated and dilution details were added. • The 48-week Treatment Period was changed to a 56 week Treatment Period and the Follow-up Period was changed from 12 weeks to 4 weeks. This was due to the changed timing of last dose with subsequent change in initial follow-up to align with change in dosing interval.
02 April 2015	Exclusion criteria 4 modified to include treatment with tacrolimus, alemtuzumab, mitoxantrone and CD20 treatments.
28 September 2015	Exclusion 8 extended to include subjects requiring treatment with prednisone/prednisolone for conditions other than PV; addition of a minimum 1-year Individualized Follow-up Period for subjects who did not enroll in the extension study
25 April 2016	Criteria for maintaining subjects in the Individualized Follow-up Period were modified to allow for improved safety monitoring following last dose of study treatment, while facilitating the exit of subjects from the study to progress to alternative treatment if needed. Because the study had been terminated, text added to allow Sponsor unblinding of subjects' randomized treatment assignments. This was to provide information for the Investigators' continued monitoring of their subjects.
05 September 2016	• All mentions of GlaxoSmithKline/GSK were changed to Novartis. Legal registered and contact addresses updated. • Novartis Study IDs were added as follows: Core Study: OPV116910 (also known as COMB157J2301)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Novartis terminated the development of the PV program and this study was terminated for non-safety reasons. As described in the End Point descriptions, due to system limitations not accepting NE=not estimable, 99999 values are not valid values

Notes: