Clinical trial results:
A randomized, partial-blind, placebo-controlled trial evaluating the efficacy, safety, pharmacokinetics and pharmacodynamics of VAY736 in the treatment of patients with pemphigus vulgaris

Summary

EudraCT number	2013-001217-33
Trial protocol	AT
Global end of trial date	25 September 2019

Results information

Result version number	v1 (current)
This version publication date	10 October 2020
First version publication date	10 October 2020

Trial information

Trial identification

Sponsor protocol code	CVAY736X2203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01930175
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, 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	25 September 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 September 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to compare the efficacy of single i.v. doses of VAY736 relative to placebo in reducing clinical disease activity of pemphigus vulgaris (PV) patients, as determined by the change in Pemphigus Disease Area Index (PDAI) between baseline and 12 weeks

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	18 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	China: 2
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	13
EEA total number of subjects	7

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)	11
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 13 participants were enrolled and randomized into the study from Austria (1 center); Bulgaria (1 center); Taiwan (1 center); USA (2 centers).

Pre-assignment

Screening details:

The study was planned to be conducted in approximately 32 patients. However, after enrolling 13 patients, the recruitment was terminated due to strategic reasons related to the development of the compound.

Period 1

Period 1 title	Core study
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Data analyst, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	VAY736 3 mg/kg

Arm description:

single dose iv of VAY736 at a dose of 3mg/kg

Arm type	Experimental
Investigational medicinal product name	VAY736
Investigational medicinal product code	
Other name	Ianalumab
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

single dose iv of VAY736 at a dose of 3mg/kg

Arm title	VAY736 10 mg/kg

Arm description:

single dose iv of VAY736 at a dose of 10mg/kg initiated following a safety review of patients receiving VAY736 3 mg/kg or placebo

Arm type	Experimental
Investigational medicinal product name	VAY736
Investigational medicinal product code	
Other name	Ianalumab
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

single dose iv of VAY736 at a dose of 10mg/kg initiated following a safety review of patients receiving VAY736 3 mg/kg or placebo.

Arm title	Placebo

Arm description:

single dose iv of Placebo

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

single dose iv of Placebo

Number of subjects in period 1	VAY736 3 mg/kg	VAY736 10 mg/kg	Placebo
Started	7	2	4
Safety analysis set	7	2	4
Pharmacokinetics (PK) analysis set	7	2	0 [1]
Completed	7	1	3
Not completed	0	1	1
Adverse event, non-fatal	-	-	1
Lost to follow-up	-	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: patients not analysed for PK

Period 2

Period 2 title	Open Label VAY736 10 mg/kg at Week 24
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Patients randomized to placebo in period 1 received open label VAY736 10mg/kg at week 24.

Arms

Arm title	Placebo

Arm description:

single dose iv of Placebo

Arm type	Placebo
Investigational medicinal product name	VAY736 10 mg/kg
Investigational medicinal product code	
Other name	Ianalumab
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

single dose iv of VAY736 at a dose of 10mg/kg at week 24

Number of subjects in period 2[2]	Placebo
Started	3
Completed	3

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Only patients randomized to Placebo in Period 1

Baseline characteristics

Reporting groups	
Reporting group title	VAY736 3 mg/kg
Reporting group description:	
single dose iv of VAY736 at a dose of 3mg/kg	
Reporting group title	VAY736 10 mg/kg
Reporting group description:	
single dose iv of VAY736 at a dose of 10mg/kg initiated following a safety review of patients receiving VAY736 3 mg/kg or placebo	
Reporting group title	Placebo
Reporting group description:	
single dose iv of Placebo	

Reporting group values	VAY736 3 mg/kg	VAY736 10 mg/kg	Placebo
Number of subjects	7	2	4
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	2	3
From 65-84 years	1	0	1
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	51.6	35.0	56.0
standard deviation	± 10.45	± 8.49	± 8.83
Sex: Female, Male Units: Participants			
Female	3	0	2
Male	4	2	2
Race/Ethnicity, Customized Units: Subjects			
Asian	2	1	1
Caucasian	4	1	3
Other	1	0	0

Reporting group values	Total		
Number of subjects	13		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	11		
From 65-84 years	2		
85 years and over	0		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Participants			
Female	5		
Male	8		
Race/Ethnicity, Customized			
Units: Subjects			
Asian	4		
Caucasian	8		
Other	1		

End points

End points reporting groups

Reporting group title	VAY736 3 mg/kg
Reporting group description: single dose iv of VAY736 at a dose of 3mg/kg	
Reporting group title	VAY736 10 mg/kg
Reporting group description: single dose iv of VAY736 at a dose of 10mg/kg initiated following a safety review of patients receiving VAY736 3 mg/kg or placebo	
Reporting group title	Placebo
Reporting group description: single dose iv of Placebo	
Reporting group title	Placebo
Reporting group description: single dose iv of Placebo	

Primary: Pemphigus Disease Area Index (PDAI) at week 12

End point title	Pemphigus Disease Area Index (PDAI) at week 12[1]

End point description:

PDAI is specific cutaneous and mucosal disease activity assessment performed by investigator based on evaluation of lesions in well-defined anatomical locations. The score weighted for the number and size of lesions with score of 0 (absent) to 10 given for skin (12 body locations), scalp and mucous membrane showing disease activity (erosions/blisters or new erythema). Damage, such as post inflammatory hyperpigmentation or erythema from resolving lesion, scored separately from the main score as absent (0) or present (1) for each body area or scalp resulting in a score of 0 to 12 or 0 to 1, respectively. Thus, PDAI ranged from 0 to 263, with 250 points representing disease activity (120 points for skin activity; 10 points for scalp activity; 120 points for mucosal activity) and 13 points representing disease damage. No statistical analysis was performed as the study was terminated.

End point type	Primary

End point timeframe:

Week 12

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 statistical analysis was performed as the study was terminated.

End point values	VAY736 3 mg/kg	VAY736 10 mg/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	2	3	
Units: Score on the scale				
arithmetic mean (standard deviation)	5.90 (± 1.836)	10.15 (± 8.273)	22.07 (± 25.628)	

Statistical analyses

No statistical analyses for this end point

Secondary: Autoimmune Skin disease Intensity Score (ABSIS) at baseline and week 12.

End point title	Autoimmune Skin disease Intensity Score (ABSIS) at baseline and week 12.

End point description:

The ABSIS Score is a quality- and quantity-based score for cutaneous and oral mucosal lesions combining the extent of the affected body surface area (BSA), the quality of the skin lesions and oral involvement. The ABSIS score ranged from 0 to 206 with 150 points for skin involvement, 11 points for oral involvement and 45 points for subjective discomfort during eating and drinking. A reduction from baseline (or, a negative change from baseline) in ABSIS indicates improvement in patients.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	VAY736 3 mg/kg	VAY736 10 mg/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	2	4	
Units: Score on the scale				
arithmetic mean (standard deviation)				
Baseline	13.26 (± 7.621)	16.38 (± 12.905)	33.75 (± 21.620)	
Week 12	2.19 (± 3.465)	5.55 (± 7.707)	16.17 (± 25.838)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Investigator Global Assessment (IGA) at week 12

End point title	Change from baseline in Investigator Global Assessment (IGA) at week 12

End point description:

The IGA score ranges from 0 to 4 and the decrease or reduction from baseline in IGA score indicates improvement in patients.
IGA score scale:
0=Clear, 1=Near Clear, 2=Mild, 3=Moderate, 4=Severe active disease

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	VAY736 3 mg/kg	VAY736 10 mg/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	2	3	
Units: Score on the scale				
arithmetic mean (standard deviation)	-1.4 (± 0.79)	-1.0 (± 0.00)	-0.7 (± 0.58)	

Statistical analyses

No statistical analyses for this end point

Secondary: VAY736 Serum Concentration - AUCinf

End point title	VAY736 Serum Concentration - AUCinf

End point description:

The area under the serum concentration-time curve from time zero to infinity [mass × time / volume]. The concentration of VAY736 was measured in the serum.

End point type	Secondary

End point timeframe:

predose, 2, 24 hours and weeks 1, 2, 3, 6, 9, 12, 16, 20, 24 and approximately 52 weeks

End point values	VAY736 3 mg/kg	VAY736 10 mg/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	2	0[2]	
Units: day*ug/mL				
arithmetic mean (standard deviation)	440 (± 114)	1480 (± 231)	()	

Notes:

[2] - PK not analyzed for placebo arm

Statistical analyses

No statistical analyses for this end point

Secondary: VAY736 Serum Concentration - AUClast

End point title	VAY736 Serum Concentration - AUClast

End point description:

The area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration [mass × time / volume]. The concentration of VAY736 was measured in the serum.

End point type	Secondary

End point timeframe:

predose, 2, 24 hours and weeks 1, 2, 3, 6, 9, 12, 16, 20, 24 and approximately 52 weeks

End point values	VAY736 3 mg/kg	VAY736 10 mg/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	2	0[3]	
Units: day*ug/mL				
arithmetic mean (standard deviation)	440 (± 114)	1480 (± 231)	()	

Notes:

[3] - PK not analyzed for placebo arm

Statistical analyses

No statistical analyses for this end point

Secondary: VAY736 Serum Concentration - Cmax

End point title	VAY736 Serum Concentration - Cmax

End point description:

The observed maximum serum concentration following drug administration [mass / volume]. The concentration of VAY736 was measured in the serum.

End point type	Secondary

End point timeframe:

predose, 2, 24 hours and weeks 1, 2, 3, 6, 9, 12, 16, 20, 24 and approximately 52 weeks

End point values	VAY736 3 mg/kg	VAY736 10 mg/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	2	0[4]	
Units: ug/mL				
arithmetic mean (standard deviation)	77.1 (± 13.0)	230 (± 2.83)	()	

Notes:

[4] - PK not analyzed for placebo arm

Statistical analyses

No statistical analyses for this end point

Secondary: VAY736 Serum Concentration - Tmax

End point title	VAY736 Serum Concentration - Tmax

End point description:

Tmax is the time to reach the maximum concentration after drug administration [time]. The concentration of VAY736 was
measured in the serum.

End point type	Secondary

End point timeframe:

predose, 2, 24 hours and weeks 1, 2, 3, 6, 9, 12, 16, 20, 24 and approximately 52 weeks

End point values	VAY736 3 mg/kg	VAY736 10 mg/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	2	0[5]	
Units: Hours				
median (full range (min-max))	2.05 (2.00 to 2.22)	2.11 (2.00 to 2.22)	(to)	

Notes:

[5] - PK not analyzed for placebo arm

Statistical analyses

No statistical analyses for this end point

Secondary: VAY736 Serum Concentration - T1/2

End point title	VAY736 Serum Concentration - T1/2

End point description:

T1/2 is the terminal elimination half-life [time]. The concentration of VAY736 was measured in the serum.

End point type	Secondary

End point timeframe:

predose, 2, 24 hours and weeks 1, 2, 3, 6, 9, 12, 16, 20, 24 and approximately 52 weeks

End point values	VAY736 3 mg/kg	VAY736 10 mg/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	2	0[6]	
Units: Days				
arithmetic mean (standard deviation)	11.2 (± 2.01)	15.4 (± 1.93)	()	

Notes:

[6] - PK not analyzed for placebo arm

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected from first dose of study treatment until end of study for up to 5 years.	
Adverse event reporting additional description:	
Any sign or symptom until end of study for up to 5 years.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	VAY736 3 mg/kg
Reporting group description:	
VAY736 3 mg/kg	
Reporting group title	Placebo
Reporting group description:	
Placebo	
Reporting group title	Open label VAY736 10 mg/kg
Reporting group description:	
Patients randomized to placebo in period 1 received open label VAY736 10mg/kg at week 24	
Reporting group title	VAY736 10 mg/kg
Reporting group description:	
VAY736 10 mg/kg	

Serious adverse events	VAY736 3 mg/kg	Placebo	Open label VAY736 10 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	1 / 4 (25.00%)	1 / 3 (33.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenal ulcer			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Pemphigus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	VAY736 10 mg/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Eye disorders			
Cataract			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Duodenal ulcer			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Pemphigus			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	VAY736 3 mg/kg	Placebo	Open label VAY736 10 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 7 (85.71%)	3 / 4 (75.00%)	3 / 3 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Vascular disorders			

Orthostatic hypotension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Influenza like illness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 7 (42.86%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Dysphonia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	2 / 7 (28.57%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	3	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			

Insomnia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	6	0	0
Investigations			
Amylase increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Blood bilirubin increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Blood calcium decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Blood magnesium decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Blood potassium increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Lipase increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Headache			

subjects affected / exposed	2 / 7 (28.57%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	2	0	1
Sciatica			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Flatulence			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Gingival recession			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Oral pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Dermatitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Mechanical urticaria			

subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Osteoarthritis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Dermatophytosis of nail			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Herpes simplex			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Impetigo			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Laryngitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			

subjects affected / exposed	1 / 7 (14.29%)	1 / 4 (25.00%)	1 / 3 (33.33%)
occurrences (all)	2	1	1
Oral fungal infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Otitis media			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Paronychia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Tooth abscess			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0

Non-serious adverse events	VAY736 10 mg/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		

Fatigue subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Influenza like illness subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Pain subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1		
Pyrexia subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Dysphonia subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Dyspnoea subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1		
Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Investigations Amylase increased subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		

Blood bilirubin increased subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Blood calcium decreased subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Blood magnesium decreased subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Blood potassium increased subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Lipase increased subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1		
Cardiac disorders Arrhythmia subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1		
Headache subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 2		
Sciatica subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 2		
Eye disorders Conjunctivitis allergic			

subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Flatulence subjects affected / exposed occurrences (all) Gingival recession subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Oral pain subjects affected / exposed occurrences (all) Toothache subjects affected / exposed occurrences (all)	 0 / 2 (0.00%) 0 0 / 2 (0.00%) 0 0 / 2 (0.00%) 0 0 / 2 (0.00%) 0 0 / 2 (0.00%) 0 0 / 2 (0.00%) 0		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Dermatitis subjects affected / exposed occurrences (all) Mechanical urticaria subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 0 / 2 (0.00%) 0 0 / 2 (0.00%) 0 0 / 2 (0.00%) 0 0 / 2 (0.00%) 0		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Osteoarthritis			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Dermatophytosis of nail			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Herpes simplex			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Impetigo			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Laryngitis			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Oral fungal infection			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Otitis media			

subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Paronychia			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Tooth abscess			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 April 2014	This protocol was amended to address comments received from review by country Health Authorities and Ethics Committees. The amendment clarified the randomization range and the use of standard of care (SoC) medication. Wording was added to clarify the purpose of the Safety Data Review Committee. Minor protocol text inconsistencies were corrected.
13 September 2016	The protocol was amended to implement a change in the safety follow up strategy in order to lower patient burden by reducing the frequency of safety follow-up visits and the assessments during these visits whilst still ensuring appropriate safety-follow-up of the patients. The follow-up visit frequency was reduced from once every 12 weeks to once every 24 weeks after one year (week 52) of follow-up and after 2 years (week 100) reduced from once every 12 weeks to once every 48 weeks.
04 November 2016	The purpose of this amendment was to include measurement of immunoglobulin (Ig) and immunoglobulin subsets in the safety follow-up. It was reported that in a few patients who experienced a severe infection after chronic rituximab treatment (a drug that has similar mode of action than VAY736), early reductions in IgG levels in association with concomitant treatment with high dose glucocorticoids were factors associated with late onset severe infections. Although the patients in this study have received only a single dose of VAY736, monitoring of total immunoglobulin and immunoglobulin subsets levels may provide additional information on safety of patients following VAY736 treatment. At this stage, all patients, the Investigator and Novartis have been open label, as all have completed the double blind Week 24 treatment period.
09 April 2019	The protocol was amended to allow for study termination 2 years after last VAY736 dose. Based on the review of the most recent data from the current study as well as from other VAY736 treated patients enrolled in other clinical studies (261 treated with VAY736), it was not considered necessary to continue for the present study a follow-up of the patients beyond 2 years.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported