

**Clinical trial results:**

A single dose, double-blind, placebo-controlled, parallel study to assess the pharmacodynamics, pharmacokinetics and safety and tolerability of VAY736 in patients with primary Sjögren's syndrome

Summary

EudraCT number	2013-000250-22
Trial protocol	DE
Global end of trial date	07 February 2018

Results information

Result version number	v1 (current)
This version publication date	08 February 2019
First version publication date	08 February 2019

Trial information**Trial identification**

Sponsor protocol code	CVAY736X2201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02149420
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	07 February 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	07 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of a single iv dose VAY736 versus placebo on the clinical disease activity of primary Sjögren's syndrome patients as measured by the change of a modified EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) between Base line and Week 12. To assess the safety and tolerability of a single iv dose VAY736 in patients with primary Sjögren's syndrome as measured by adverse events (AEs).

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	23 May 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	Germany: 27
Worldwide total number of subjects	27
EEA total number of subjects	27

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)	23
From 65 to 84 years	4

Subject disposition

Recruitment

Recruitment details:

A total of 27 patients were enrolled and randomized into the study at one site in Germany.

Pre-assignment

Screening details:

The patients were enrolled in 2 sequential cohorts:

Cohort 1: Six patients were randomized to receive a single dose iv of VAY736 at a dose of 3mg/kg or placebo at a 2:1 ratio.

Cohort 2: Twenty one patients were randomized to receive a single iv dose of VAY736 at a dose of 10.0 mg/kg or 3.0 mg/kg or placebo at a 6:1:3 ratio.

Period 1

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

Blinding implementation details:

This was a double-blind study for the duration of the treatment period (weeks 0-24), following which, treatment was unblinded on an individual patient level to determine their progress in the study (Follow-up, open-label VAY736 or EOS Visit).

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

single dose iv of Placebo (+ Option to receive Open label VAY736 10 mg/kg at Week 24)

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

single i.v. dose from infusion bag lacking active compound

Arm title	VAY736 3 mg/kg
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Arm description:

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

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

Dosage and administration details:

single iv dose of 3 mg/kg VAY736 from infusion bag containing the active compound

Arm title	VAY736 10 mg/kg
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Arm description:

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

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

Dosage and administration details:

single iv dose of 10 mg/kg VAY736 from infusion bag containing the active compound

Number of subjects in period 1	Placebo	VAY736 3 mg/kg	VAY736 10 mg/kg
Started	9	6	12
Safety analysis set	9	6	12
Completed	9	5	10
Not completed	0	1	2
Administrative problems	-	1	2

Period 2

Period 2 title	Open Label VAY736 10 mg/kg Extension
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Placebo - switched to open label VAY736
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Arm description:

single dose iv of Placebo (+ Option to receive Open label VAY736 10 mg/kg at Week 24)

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

Dosage and administration details:

single iv dose of 10 mg/kg VAY736 from infusion bag containing the active compound

Number of subjects in period 2 ^[1]	Placebo - switched to open label VAY736
Started	5
Completed	4
Not completed	1
Administrative problems	1

Notes:

[1] - 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 were eligible to enter.

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: single dose iv of Placebo (+ Option to receive Open label VAY736 10 mg/kg at Week 24)	
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	

Reporting group values	Placebo	VAY736 3 mg/kg	VAY736 10 mg/kg
Number of subjects	9	6	12
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)	9	6	8
From 65-84 years	0	0	4
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	46.7	46.8	55.3
standard deviation	± 11.29	± 8.75	± 13.35
Sex: Female, Male			
Units: Subjects			
Female	7	5	11
Male	2	1	1
Race/Ethnicity, Customized			
Units: Subjects			

Reporting group values	Total		
Number of subjects	27		
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)	23		
From 65-84 years	4		
85 years and over	0		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Subjects			
Female	23		
Male	4		
Race/Ethnicity, Customized			
Units: Subjects			

Subject analysis sets

Subject analysis set title	VAY736 Combined
Subject analysis set type	Full analysis
Subject analysis set description: Combining VAY736 3mg/kg and VAY736 10mg/kg	
Subject analysis set title	Open label VAY736
Subject analysis set type	Full analysis
Subject analysis set description: Open label VAY736 10mg/kg	

Reporting group values	VAY736 Combined	Open label VAY736	
Number of subjects	18	5	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	14	5	
From 65-84 years	4	0	
85 years and over	0	0	
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	±	±	
Sex: Female, Male			
Units: Subjects			
Female			
Male			

Race/Ethnicity, Customized			
Units: Subjects			

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: single dose iv of Placebo (+ Option to receive Open label VAY736 10 mg/kg at Week 24)	
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	
Reporting group title	Placebo - switched to open label VAY736
Reporting group description: single dose iv of Placebo (+ Option to receive Open label VAY736 10 mg/kg at Week 24)	
Subject analysis set title	VAY736 Combined
Subject analysis set type	Full analysis
Subject analysis set description: Combining VAY736 3mg/kg and VAY736 10mg/kg	
Subject analysis set title	Open label VAY736
Subject analysis set type	Full analysis
Subject analysis set description: Open label VAY736 10mg/kg	

Primary: Change in EULAR Sjögren's syndrome disease activity index (ESSDAI)

End point title	Change in EULAR Sjögren's syndrome disease activity index (ESSDAI)
End point description: The effect of VAY736 on clinical disease activity was measured by the change in ESSDAI (EULAR Sjögren's syndrome disease activity index) between baseline and week 12. The instrument contains 12 organ-specific domains contributing to disease activity. For each domain, features of disease activity are scored in 3 or 4 levels according to their severity. These scores are then summed across the 12 domains in a weighted manner to provide the total score (range 0-123). A reduction from baseline indicates improvement in patients.	
End point type	Primary
End point timeframe: Baseline, week 12	

End point values	Placebo	VAY736 3 mg/kg	VAY736 10 mg/kg	VAY736 Combined
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	9	6	12	18
Units: Points				
arithmetic mean (standard deviation)				
Baseline	11.1 (± 4.08)	14.5 (± 9.44)	11.5 (± 4.38)	12.5 (± 6.38)
Week 12	10.2 (± 5.29)	10.7 (± 7.69)	10.0 (± 5.36)	10.2 (± 6.01)
Change from Baseline to Week 12	-0.9 (± 2.98)	-3.8 (± 8.66)	-1.5 (± 3.00)	-2.3 (± 5.40)

Statistical analyses

Statistical analysis title	Change in ESSDAI
Statistical analysis description:	
Per protocol the primary analysis was between placebo and the combined VAY736 groups at Week 12.	
Comparison groups	Placebo v VAY736 Combined
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.678
Method	repeated measures Bayesian analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.007
upper limit	3.18
Variability estimate	Standard deviation
Dispersion value	2.058

Primary: Overall incidence of Adverse Events

End point title	Overall incidence of Adverse Events ^[1]
End point description:	
Number of subjects with Adverse Events during the double blind treatment period.	
End point type	Primary
End point timeframe:	
Baseline to Week 24	

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 analyses were calculated.

End point values	Placebo	VAY736 3 mg/kg	VAY736 10 mg/kg	VAY736 Combined
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	9	6	12	18
Units: Participants				
Subjects with AEs	8	6	11	17
Subjects with AEs within 24hr	2	6	11	17
Subjects with AEs post 24hr	8	6	8	14
Subjects with Study drug-related AEs	5	6	11	17
Subjects with Infusion related AEs	1	6	9	15

Statistical analyses

No statistical analyses for this end point

Secondary: Change in EULAR Sjögren's Syndrome Patient Response Index (ESSPRI)

End point title	Change in EULAR Sjögren's Syndrome Patient Response Index (ESSPRI)
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End point description:

The ESSPRI is a patient self-reported outcome measure to assess dryness, limb pain, fatigue and mental fatigue, where each of the domains normally reported as 0 (not at all) to 10 (extremely severe). The final ESSPRI score is the average of three: dryness, pain and fatigue. A reduction from baseline indicates the improvement of symptoms. During the study all individual scores were reported as 1 to 10 instead. A linear transformation was reported to map the scores to the range of 0-10.

End point type	Secondary
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End point timeframe:

Baseline, week 12

End point values	Placebo	VAY736 3 mg/kg	VAY736 10 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	6	12	
Units: Points				
arithmetic mean (standard deviation)				
Baseline	5.967 (± 2.2179)	6.049 (± 1.2759)	6.235 (± 1.5379)	
Week 12	5.926 (± 1.5822)	6.173 (± 1.4753)	4.568 (± 2.5966)	
Change from Baseline to Week 12	-0.041 (± 1.7805)	0.123 (± 1.0120)	-1.667 (± 1.8918)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Short Form (36) Health Survey (SF-36)

End point title	Change in Short Form (36) Health Survey (SF-36)
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End point description:

The SF-36 is a 36-item, patient self-reported outcome measure (questionnaires) of patient health. The outcome of the questionnaires in eight scales results in two summary scores, physical component and mental component, both ranging from 0 - 100. An increase from baseline in either component summary score indicates reduced disease burden.

End point type	Secondary
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End point timeframe:

Baseline, week 12

End point values	Placebo	VAY736 3 mg/kg	VAY736 10 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	6	12	
Units: Points				
arithmetic mean (standard deviation)				
Physical component score: Baseline	46.886 (± 6.3905)	39.445 (± 4.2857)	46.015 (± 9.3533)	
Physical component score: Week 12	44.788 (± 8.3513)	45.493 (± 7.3060)	47.671 (± 9.2804)	
Physical component score: Change from Baseline	-2.098 (± 7.9084)	6.048 (± 4.7189)	1.656 (± 5.4113)	
Mental component score: Baseline	36.913 (± 15.2776)	37.517 (± 6.8994)	43.628 (± 11.3667)	
Mental component score: Week 12	41.012 (± 13.2991)	40.170 (± 11.9815)	46.700 (± 11.3182)	
Mental component score: Change from Baseline	4.099 (± 5.3361)	2.653 (± 17.1261)	3.073 (± 11.5823)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Multidimensional Fatigue Inventory (MFI)

End point title	Change in Multidimensional Fatigue Inventory (MFI)
End point description:	The MFI is a patient self-reported outcome measure (questionnaires) to assess fatigue covering the following dimensions: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation and Reduced Activity. Each dimension has a possible range from 4-20. A reduction from baseline in MFI indicates improvement.
End point type	Secondary
End point timeframe:	Baseline, week 12

End point values	Placebo	VAY736 3 mg/kg	VAY736 10 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	6	12	
Units: Points				
arithmetic mean (standard deviation)				
General Fatigue: Baseline	14.0 (± 4.72)	17.0 (± 2.37)	15.9 (± 3.34)	
General Fatigue: Week 12	12.8 (± 4.84)	14.2 (± 6.40)	12.4 (± 3.99)	
General Fatigue: Change from Baseline	-1.2 (± 1.64)	-2.8 (± 5.04)	-3.5 (± 4.12)	
Physical Fatigue: Baseline	12.9 (± 4.14)	15.7 (± 2.34)	14.2 (± 3.41)	

Physical Fatigue: Week 12	12.2 (± 3.99)	11.2 (± 5.15)	10.4 (± 4.66)	
Physical Fatigue: Change from Baseline	-0.7 (± 1.32)	-4.5 (± 6.57)	-3.8 (± 4.77)	
Mental Fatigue: Baseline	11.9 (± 4.78)	14.3 (± 3.78)	13.0 (± 3.28)	
Mental Fatigue: Week 12	11.7 (± 4.12)	11.3 (± 4.18)	9.8 (± 5.17)	
Mental Fatigue: Change from Baseline	-0.2 (± 2.95)	-3.0 (± 6.07)	-3.2 (± 5.84)	
Reduced motivation: Baseline	12.4 (± 4.93)	12.3 (± 3.93)	10.9 (± 2.68)	
Reduced motivation: Week 12	12.0 (± 5.32)	10.0 (± 4.52)	9.8 (± 4.97)	
Reduced motivation: Change from Baseline	-0.4 (± 2.40)	-2.3 (± 4.50)	-1.1 (± 4.56)	
Reduced activity: Baseline	11.8 (± 2.86)	10.8 (± 1.72)	12.2 (± 2.69)	
Reduced activity: Week 12	10.4 (± 3.81)	8.7 (± 3.61)	9.3 (± 5.08)	
Reduced activity: Change from Baseline	-1.3 (± 1.80)	-2.2 (± 4.83)	-2.9 (± 4.25)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the physician's global assessment by means of Visual Analog Scale (VAS)

End point title	Change in the physician's global assessment by means of Visual Analog Scale (VAS)
End point description:	The visual analogue scale used is a 100 mm VAS ranging from "no disease" (0 mm) to "maximal disease activity" (100 mm).
End point type	Secondary
End point timeframe:	Baseline, week 12

End point values	Placebo	VAY736 3 mg/kg	VAY736 10 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	6	12	
Units: Points				
arithmetic mean (standard deviation)				
Baseline	57.3 (± 17.73)	66.2 (± 17.53)	65.0 (± 11.74)	
Week 12	59.8 (± 23.35)	43.0 (± 23.82)	48.5 (± 17.33)	
Change from Baseline to Week 12	2.4 (± 12.21)	-23.2 (± 31.10)	-16.5 (± 18.96)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the patient's global assessment by means of Visual Analog Scale (VAS)

End point title	Change in the patient's global assessment by means of Visual Analog Scale (VAS)
End point description: The visual analogue scale used is a 100 mm VAS ranging from "no disease" (0 mm) to "maximal disease activity" (100 mm).	
End point type	Secondary
End point timeframe: Baseline, week 12	

End point values	Placebo	VAY736 3 mg/kg	VAY736 10 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	6	12	
Units: Points				
arithmetic mean (standard deviation)				
Baseline	56.2 (± 24.86)	67.2 (± 13.69)	59.8 (± 24.30)	
Week 12	55.2 (± 21.57)	44.2 (± 22.75)	40.8 (± 20.49)	
Change from Baseline to Week 12	-1.0 (± 17.71)	-23.0 (± 25.73)	-19.0 (± 21.08)	

Statistical analyses

No statistical analyses for this end point

Secondary: VAY736 serum concentration - AUCinf

End point title	VAY736 serum concentration - AUCinf ^[2]
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: 0, 1, 2, 3, 6, 9, 12, 16, 20, 24 and approximately 52 weeks.	

Notes:

[2] - 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: PK was not assessed for Placebo

End point values	VAY736 3 mg/kg	VAY736 10 mg/kg	Open label VAY736	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	12	5	
Units: day*ug/mL				
median (full range (min-max))	389 (186 to 457)	1140 (515 to 1610)	971 (849 to 1340)	

Statistical analyses

No statistical analyses for this end point

Secondary: VAY736 serum concentration - AUClast

End point title | VAY736 serum concentration - AUClast^[3]

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:

0, 1, 2, 3, 6, 9, 12, 16, 20, 24 and approximately 52 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: PK was not assessed for Placebo

End point values	VAY736 3 mg/kg	VAY736 10 mg/kg	Open label VAY736	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	12	5	
Units: day*ug/mL				
median (full range (min-max))	385 (184 to 457)	1140 (514 to 1610)	971 (848 to 1340)	

Statistical analyses

No statistical analyses for this end point

Secondary: VAY736 serum concentration - CL

End point title | VAY736 serum concentration - CL^[4]

End point description:

The systemic (or total body) clearance from serum following intravenous administration [volume / time]. The concentration of VAY736 was measured in the serum.

End point type | Secondary

End point timeframe:

0, 1, 2, 3, 6, 9, 12, 16, 20, 24 and approximately 52 weeks.

Notes:

[4] - 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: PK was not assessed for Placebo

End point values	VAY736 3 mg/kg	VAY736 10 mg/kg	Open label VAY736	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	12	5	
Units: L/day				
median (full range (min-max))	0.594 (0.427 to 0.844)	0.584 (0.550 to 1.30)	0.686 (0.427 to 0.750)	

Statistical analyses

No statistical analyses for this end point

Secondary: VAY736 serum concentration - Cmax

End point title VAY736 serum concentration - Cmax^[5]

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:

0, 1, 2, 3, 6, 9, 12, 16, 20, 24 and approximately 52 weeks.

Notes:

[5] - 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: PK was not assessed for Placebo

End point values	VAY736 3 mg/kg	VAY736 10 mg/kg	Open label VAY736	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	12	5	
Units: ug/mL				
median (full range (min-max))	65.0 (45.4 to 76.5)	213 (150 to 283)	205 (174 to 217)	

Statistical analyses

No statistical analyses for this end point

Secondary: VAY736 serum concentration - T1/2

End point title VAY736 serum concentration - T1/2^[6]

End point description:

Apparent terminal half-life, determined as the $\ln 2 / \lambda_z$ or $0.693 / \lambda_z$. The concentration of VAY736 was measured in the serum.

End point type Secondary

End point timeframe:

0, 1, 2, 3, 6, 9, 12, 16, 20, 24 and approximately 52 weeks.

Notes:

[6] - 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: PK was not assessed for Placebo

End point values	VAY736 3 mg/kg	VAY736 10 mg/kg	Open label VAY736	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	12	5	
Units: days				
median (full range (min-max))	8.43 (6.99 to 13.8)	9.51 (5.38 to 15.2)	11.0 (4.94 to 17.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: VAY736 serum concentration - Tmax

End point title | VAY736 serum concentration - Tmax^[7]

End point description:

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:

0, 1, 2, 3, 6, 9, 12, 16, 20, 24 and approximately 52 weeks.

Notes:

[7] - 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: PK was not assessed for Placebo

End point values	VAY736 3 mg/kg	VAY736 10 mg/kg	Open label VAY736	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	12	5	
Units: hours				
median (full range (min-max))	2.03 (2.00 to 2.20)	2.03 (2.00 to 2.30)	2.10 (2.02 to 2.17)	

Statistical analyses

No statistical analyses for this end point

Secondary: VAY736 serum concentration - Vz

End point title | VAY736 serum concentration - Vz^[8]

End point description:

The volume of distribution during the terminal elimination phase following intravenous administration [volume]. The concentration of VAY736 was measured in the serum.

End point type | Secondary

End point timeframe:

0, 1, 2, 3, 6, 9, 12, 16, 20, 24 and approximately 52 weeks.

Notes:

[8] - 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: PK was not assessed for Placebo

End point values	VAY736 3 mg/kg	VAY736 10 mg/kg	Open label VAY736	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	12	5	
Units: Liter				
median (full range (min-max))	7.83 (6.55 to 10.7)	8.68 (7.15 to 12.4)	10.3 (4.93 to 18.6)	

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.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo

Reporting group title	VAY736 3mg/kg
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Reporting group description:

VAY736 3mg/kg

Reporting group title	VAY736 10mg/kg
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Reporting group description:

VAY736 10mg/kg

Reporting group title	Open label VAY736 10mg/kg
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Reporting group description:

Open label VAY736 10mg/kg

Serious adverse events	Placebo	VAY736 3mg/kg	VAY736 10mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)	2 / 6 (33.33%)	0 / 12 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Jaw fracture			
subjects affected / exposed	0 / 9 (0.00%)	1 / 6 (16.67%)	0 / 12 (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
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 6 (0.00%)	0 / 12 (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
Inguinal hernia			

subjects affected / exposed	0 / 9 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst torsion			
subjects affected / exposed	0 / 9 (0.00%)	1 / 6 (16.67%)	0 / 12 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 6 (0.00%)	0 / 12 (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

Serious adverse events	Open label VAY736 10mg/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Jaw fracture			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			

Ovarian cyst torsion subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 5 (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: 5 %

Non-serious adverse events	Placebo	VAY736 3mg/kg	VAY736 10mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	6 / 6 (100.00%)	11 / 12 (91.67%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 9 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 9 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	4
Non-cardiac chest pain			
subjects affected / exposed	2 / 9 (22.22%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 9 (0.00%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			

Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	1 / 6 (16.67%) 1	0 / 12 (0.00%) 0
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 6 (16.67%) 1	0 / 12 (0.00%) 0
Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	6 / 6 (100.00%) 6	9 / 12 (75.00%) 18
Ligament rupture subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0
Limb injury subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	3 / 9 (33.33%) 4	2 / 6 (33.33%) 3	2 / 12 (16.67%) 4
Blood and lymphatic system disorders Iron deficiency anaemia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 6 (0.00%) 0	1 / 12 (8.33%) 2
Eye disorders Chalazion subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 6 (16.67%) 1	0 / 12 (0.00%) 0
Keratitis			

subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 6 (16.67%) 1	0 / 12 (0.00%) 0
Vitreous detachment subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 6 (16.67%) 1	0 / 12 (0.00%) 0
Auriculotemporal syndrome subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 6 (16.67%) 1	0 / 12 (0.00%) 0
Noninfective sialoadenitis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0
Toothache subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0
Skin and subcutaneous tissue disorders			
Photosensitivity reaction subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 6 (0.00%) 0	1 / 12 (8.33%) 2
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	2 / 6 (33.33%) 2	0 / 12 (0.00%) 0
Back pain subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 6 (0.00%) 0	1 / 12 (8.33%) 2
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 6 (16.67%) 1	0 / 12 (0.00%) 0
Myalgia			

subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 6 (0.00%) 0	1 / 12 (8.33%) 2
Rotator cuff syndrome subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 6 (16.67%) 1	0 / 12 (0.00%) 0
Sjogren's syndrome subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	1 / 6 (16.67%) 1	0 / 12 (0.00%) 0
Synovitis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	1 / 6 (16.67%) 1	0 / 12 (0.00%) 0
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 6 (0.00%) 0	1 / 12 (8.33%) 2
Cystitis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 6 (0.00%) 0	1 / 12 (8.33%) 2
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 6 (0.00%) 0	1 / 12 (8.33%) 2
Gastrointestinal infection subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 6 (0.00%) 0	1 / 12 (8.33%) 2
Influenza subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 6 (16.67%) 1	1 / 12 (8.33%) 2
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2	5 / 6 (83.33%) 6	4 / 12 (33.33%) 12
Oral herpes subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0

Otitis media			
subjects affected / exposed	0 / 9 (0.00%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	2
Tooth infection			
subjects affected / exposed	1 / 9 (11.11%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Urogenital infection bacterial			
subjects affected / exposed	1 / 9 (11.11%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Open label VAY736 10mg/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Non-cardiac chest pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			

Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all) Ligament rupture subjects affected / exposed occurrences (all) Limb injury subjects affected / exposed occurrences (all)	3 / 5 (60.00%) 6 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2 1 / 5 (20.00%) 2		
Blood and lymphatic system disorders Iron deficiency anaemia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Eye disorders Chalazion subjects affected / exposed occurrences (all) Keratitis	0 / 5 (0.00%) 0		

<p>subjects affected / exposed occurrences (all)</p> <p>Vitreous detachment subjects affected / exposed occurrences (all)</p>	<p>0 / 5 (0.00%) 0</p> <p>1 / 5 (20.00%) 2</p>		
<p>Gastrointestinal disorders</p> <p>Abdominal pain subjects affected / exposed occurrences (all)</p> <p>Auriculotemporal syndrome subjects affected / exposed occurrences (all)</p> <p>Noninfective sialoadenitis subjects affected / exposed occurrences (all)</p> <p>Toothache subjects affected / exposed occurrences (all)</p>	<p>0 / 5 (0.00%) 0</p> <p>0 / 5 (0.00%) 0</p> <p>0 / 5 (0.00%) 0</p> <p>1 / 5 (20.00%) 2</p>		
<p>Skin and subcutaneous tissue disorders</p> <p>Photosensitivity reaction subjects affected / exposed occurrences (all)</p> <p>Rash subjects affected / exposed occurrences (all)</p>	<p>0 / 5 (0.00%) 0</p> <p>0 / 5 (0.00%) 0</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia subjects affected / exposed occurrences (all)</p> <p>Back pain subjects affected / exposed occurrences (all)</p> <p>Musculoskeletal pain subjects affected / exposed occurrences (all)</p> <p>Myalgia</p>	<p>0 / 5 (0.00%) 0</p> <p>0 / 5 (0.00%) 0</p> <p>0 / 5 (0.00%) 0</p>		

subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Rotator cuff syndrome subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Sjogren's syndrome subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2		
Synovitis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2		
Conjunctivitis subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2		
Cystitis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Gastrointestinal infection subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Influenza subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 5 (100.00%) 10		
Oral herpes subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		

Otitis media			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Tooth infection			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Urogenital infection bacterial			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 March 2015	The purpose of this amendment was to introduce the option of open-label VAY736 single dose treatment to patients that previously received placebo during the study. This change offered each patient the opportunity to receive active VAY736 treatment which has the potential to provide clinical benefits for their condition.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported