Clinical trial results:
A randomized, partially blind, placebo-controlled, proof of concept study to assess the effect of a single infusion of VAY736 on disease activity as measured by brain MRI scans in patients with relapsing-remitting multiple sclerosis

Summary

EudraCT number	2013-002324-16
Trial protocol	CZ PL
Global end of trial date	13 September 2018

Results information

Result version number	v1 (current)
This version publication date	07 September 2019
First version publication date	07 September 2019

Trial information

Trial identification

Sponsor protocol code	CVAY736X2202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02038049
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	13 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 May 2015
Global end of trial reached?	Yes
Global end of trial date	13 September 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primaty objective was to determine the effect of VAY736, compared to placebo on the cumulative number of new gadolinium [Gd]-enhancing lesions on T1-weighted brain MRI scans in patients with relapsing-remitting multiple sclerosis (RRMS).

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	20 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	Czech Republic: 1
Country: Number of subjects enrolled	Ukraine: 4
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	8
EEA total number of subjects	1

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)	8

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 5 centers in 3 countries: Czech Republic (1), Ukraine (2 sites) and USA (2 sites).

Pre-assignment

Screening details:

The study was planned to be conducted in approximately 96 patients. However, after enrolling 8 patients, the recruitment was terminated based on strategic considerations.

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	Investigator, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	VAY736

Arm description:

Intravenous infusion of VAY736

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

Dosage and administration details:

10 mg/kg i.v. infusion on Day 1

Arm title	Placebo to VAY736

Arm description:

Matching placebo (infusion bag) administered intravenously. Placebo randomized patients were offered optional VAY736 administration after week 16.

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

Dosage and administration details:

Placebo match to VAY736 10 mg/kg i.v. infusion on Day 1

Investigational medicinal product name	VAY736
Investigational medicinal product code	
Other name	Lanalumab
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo randdomized patients were offered optional VAY736 10 mg/kg i.v. infusion at week 16-17

Number of subjects in period 1	VAY736	Placebo to VAY736
Started	4	4
Pharmacodynamic (PD) analysis set	4	4
Completed	3	4
Not completed	1	0
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	VAY736
Reporting group description:	
Intravenous infusion of VAY736	
Reporting group title	Placebo to VAY736
Reporting group description:	
Matching placebo (infusion bag) administered intravenously. Placebo randomized patients were offered optional VAY736 administration after week 16.	

Reporting group values	VAY736	Placebo to VAY736	Total
Number of subjects	4	4	8
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)	4	4	8
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	32.0	42.0	
standard deviation	± 10.42	± 2.45	-
Sex: Female, Male			
Units: Subjects			
Female	2	3	5
Male	2	1	3
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	3	4	7
Other	1	0	1

End points

End points reporting groups

Reporting group title	VAY736
Reporting group description:	
Intravenous infusion of VAY736	
Reporting group title	Placebo to VAY736
Reporting group description:	
Matching placebo (infusion bag) administered intravenously. Placebo randomized patients were offered optional VAY736 administration after week 16.	
Subject analysis set title	VAY736 Administered at Visit 2 (Day 1)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Intravenous infusion of VAY736 at Visit 2 (Day 1)	
Subject analysis set title	VAY736 Administered at Visit 7 (Week 16 - Week 17)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Intravenous infusion of VAY736 at Visit 7 (Week 16 - Week 17)	
Subject analysis set title	Placebo Administered at Visit 2
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Matching placebo (infusion bag) administered intravenously at Visit 2. Placebo randomized patients were offered optional VAY736 administration after week 16.	

Primary: Cumulative number of new T1-weighted gadolinium (Gd)-enhancing lesions at Weeks 8, 12 and 16

End point title	Cumulative number of new T1-weighted gadolinium (Gd)-enhancing lesions at Weeks 8, 12 and 16[1]
End point description:	
The effect of VAY736, compared to placebo on the cumulative number of new gadolinium [Gd]-enhancing lesions on T1-weighted brain MRI scans in relapsing-remitting multiple sclerosis (RRMS) patient population at weeks 8, 12 and 16. Only descriptive statistics performed.	
End point type	Primary
End point timeframe:	
Week 8, Week 12, Week 16	

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 formal statistical analysis was conducted, the primary endpoint was summarized by treatment and listed by patient.

End point values	VAY736	Placebo to VAY736		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: Participants				
Week 8	5	1		
Week12	5	2		
Week 16	6	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of all T1-weighted gadolinium (Gd)-enhancing lesions at weeks 4, 8, 12 and 16

End point title	Number of all T1-weighted gadolinium (Gd)-enhancing lesions at weeks 4, 8, 12 and 16

End point description:

Magnetic resonance imaging (MRI) scanning of the brain was performed at screening/baseline, week 4, week 8, week 12 and week 16 to assess all T1-weighted Gadolinium (Gd) enhancing lesions. Each MRI scan was reviewed by a local neuro-radiologist. Only descriptive statistics performed.

End point type	Secondary

End point timeframe:

Week 4, Week 8, Week 12, Week 16

End point values	VAY736	Placebo to VAY736		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: Participants				
Week 4	19	2		
Week 8	20	2		
Week 12	20	3		
Week 16	21	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of new T1-weighted gadolinium (Gd)-enhancing lesions at weeks 4, 8, 12 and 16

End point title	Number of new T1-weighted gadolinium (Gd)-enhancing lesions at weeks 4, 8, 12 and 16

End point description:

Magnetic resonance imaging (MRI) scanning of the brain was performed at screening/baseline, week 4, week 8, week 12 and week 16 to assess all new T1-weighted Gadolinium (Gd) enhancing lesions. Each MRI scan was reviewed by a local neuro-radiologist. Only descriptive statistics performed.

End point type	Secondary

End point timeframe:

Week 4, Week 8, Week 12, Week 16

End point values	VAY736	Placebo to VAY736		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: Participants				
Week 4	4	1		
Week 8	1	0		
Week 12	0	1		
Week 16	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: T2 burden of disease (total volume of T2-weighted lesions) at weeks 4, 8, 12 and 16.

End point title	T2 burden of disease (total volume of T2-weighted lesions) at weeks 4, 8, 12 and 16.

End point description:

Magnetic resonance imaging (MRI) scanning of the brain was performed at screening/baseline, week 4, week 8, week 12 and week 16 to assess T2 burden of disease. Each MRI scan was reviewed by a local neuro-radiologist. Only descriptive statistics performed.

End point type	Secondary

End point timeframe:

Week 4, Week 8, Week 12, Week 16

End point values	VAY736	Placebo to VAY736		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: mm3 of T2-weighted lesions				
number (not applicable)				
Week 4	20108.9	17706		
Week 8	18998.9	16785		
Week 12	18484.1	15996		
Week 16	18102.7	17919		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects without any new MRI disease activity at weeks 4, 8, 12 and 16.

End point title	Number of subjects without any new MRI disease activity at weeks 4, 8, 12 and 16.

End point description:

Magnetic resonance imaging (MRI) scanning of the brain was performed at screening/baseline, week 4, week 8, week 12 and week 16 to assess patients without any new MRI disease activity (no new Gd-enhancing lesions nor new or enlarging T2 lesions). Each MRI scan was reviewed by a local neuro-radiologist. Only descriptive statistics performed.

End point type	Secondary

End point timeframe:

Week 4, Week 8, Week 12, Week 16

End point values	VAY736	Placebo to VAY736		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: Participants				
Week 4	4	2		
Week 8	1	0		
Week 12	0	1		
Week 16	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of relapse-free patients over the 16 weeks of the treatment period.

End point title	Proportion of relapse-free patients over the 16 weeks of the treatment period.

End point description:

A relapse is defined as the appearance of a new neurological abnormality, or worsening of previously stable, or improving pre-existing neurological abnormality, separated by at least 30 days from the onset of a preceding clinical demyelinating event. The abnormality must be present for at least 24 hours and occur in the absence of fever (<37.5 C) or infection. A relapse was considered confirmed when confirmed by an Extended disability status scale (EDSS)-certified physician who was not involved in the treatment of the patient, was blinded to treatment allocation, and had no access to patient medical records. It was recommended that this occurs within 5 days of the onset of symptoms. A relapse was confirmed when it was accompanied by an increase of at least half a point (0.5) on the EDSS or an increase of 1 point on two different Functional Systems (FS) of the EDSS or 2 points on one of the FS (excluding Bowel/Bladder or Cerebral FS). Only descriptive statistics performed.

End point type	Secondary

End point timeframe:

Week 0 (Day 1), Week 4, Week 8, Week 12, Week 16

End point values	VAY736	Placebo to VAY736		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: Participants				
Week 0 (Day 1)|Relapse-free	4	4		
Week 4|Relapse-free	4	4		
Week 8|Relapse-free	4	4		
Week 12|Relapse-free	4	4		
Week 16|Relapse-free	3	3		
Week 0 (Day 1)|Relapse	0	0		
Week 4|Relapse	0	0		
Week 8|Relapse	0	0		
Week 12|Relapse	0	0		
Week 16|Relapse	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of new or enlarging T2-weighted gadolinium (Gd)-enhancing lesions at weeks 4, 8, 12 and 16

End point title	Number of new or enlarging T2-weighted gadolinium (Gd)-enhancing lesions at weeks 4, 8, 12 and 16

End point description:

Magnetic resonance imaging (MRI) scanning of the brain was performed at screening/baseline, week 4, week 8, week 12 and week 16 to assess T2 hyperintense lesions (new or enlarging T2-weighted lesions). Each MRI scan was reviewed by a local neuro-radiologist. Only descriptive statistics performed.

End point type	Secondary

End point timeframe:

Week 4, Week 8, Week 12, Week 16

End point values	VAY736	Placebo to VAY736		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: Participants				
Week 4	279	94		
Week 8	277	93		
Week 12	276	91		
Week 16	264	91		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with On-Treatment Adverse Events, Serious Adverse Event, and Death

End point title	Number of Participants with On-Treatment Adverse Events, Serious Adverse Event, and Death

End point description:

Analysis of absolute and relative frequencies for treatment emergent Adverse Event (AE), Serious Adverse Event (SAE) and Deaths by primary System Organ Class (SOC) to demonstrate that VAY736 is safe for the treatment of patients with relapsing-remitting multiple sclerosis through the monitoring of relevant clinical and laboratory safety parameters. Only descriptive statistics performed.

End point type	Secondary

End point timeframe:

From first dosing (single administration, Day 1) up to End of Study Visit (EOS) depending on B cell recovery

End point values	VAY736 Administered at Visit 2 (Day 1)	VAY736 Administered at Visit 7 (Week 16 - Week 17)	Placebo Administered at Visit 2	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	4	4	4	
Units: Participants				
On-treatment Adverse Events (AEs)	4	3	1	
On-treatment Serious Adverse Events (SAEs)	0	0	0	
On-treatment Deaths	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events and serious adverse events were collected from first dosing (single administration, Day 1) up to End of Study Visit (EOS) depending on B cell recovery.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	VAY736 Administered at Visit 2 (Day 1)

Reporting group description:

VAY736 Administered at Visit 2 (Day 1)

Reporting group title	VAY736 Administered at Visit 7 (Week 16 - Week 17)

Reporting group description:

VAY736 Administered at Visit 7 (Week 16 - Week 17)

Reporting group title	Placebo Administered at Visit 2

Reporting group description:

Placebo Administered at Visit 2

Serious adverse events	VAY736 Administered at Visit 2 (Day 1)	VAY736 Administered at Visit 7 (Week 16 - Week 17)	Placebo Administered at Visit 2
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	VAY736 Administered at Visit 2 (Day 1)	VAY736 Administered at Visit 7 (Week 16 - Week 17)	Placebo Administered at Visit 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	3 / 4 (75.00%)	1 / 4 (25.00%)
Investigations			
Glucose urine present			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			

Infusion related reaction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Road traffic accident			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Tachycardia			
subjects affected / exposed	3 / 4 (75.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 4 (75.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	3	1	1
Hypotonia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 4 (50.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Chills			
subjects affected / exposed	2 / 4 (50.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Hyperthermia			

subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 4 (75.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	3	1	0
Vomiting			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0

Infections and infestations			
Respiratory tract infection viral			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 March 2014	Amendment 1: • Addressed a comment raised by the Czech Health Authority (Státní ústav pro kontrolu léčiv, SÚKL). For Czech Republic only: Patients may stop their current treatment (to fulfill exclusion criteria 5) only if it is considered not effective, not safe, or not tolerated by a health care professional and/or the patient. • Clarified that the total dose of paracetamol / acetaminophen should not exceed 4'000 mg within the implicated 24-hour cycle. • Corrected a typo in the example provided for H1 receptor blocker administration prior to infusion. • Corrected an inconsistency, i.e. use of H1/H2 receptor blockers rather than H1 only. • Captured changes in study personnel.
25 April 2014	Amendment 2: • Addressed a request from the Czech Health Authority (Státní ústav pro kontrolu léčiv, SÚKL). In the Czech Republic it is required that the relapse treatment for multiple sclerosis is initiated within 5 days of onset of relapse symptoms. • Captured a change in study personnel.
24 August 2017	Amendment 3: • The follow-up visit frequency was reduced from once every 12 weeks to once every 24 weeks after week 144 for VAY736 group or after week 148 for the placebo group receiving an optional VAY736 dose. • During the long-term safety follow-up visits after week 144/week 148, assessments were reduced to CD19+ B-cell count, hematology, pharmacokinetics (PK), immunoglobulin (Ig). • The cut-off used as a criterion to define B-cell recovery was defined as ≥ 50 cells/µL or within 20% of their baseline level.

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.

After enrolling 8 patients, the recruitment was terminated based on strategic considerations.

Notes: