NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Ianalumab / VAY736

Trial Indication(s)

Primary Sjögren's syndrome (pSS)

Protocol Number

CVAY736X2201

Protocol Title

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

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase 2

Study Start/End Dates

Study Start Date: May 2014 (Actual)
Primary Completion Date: February 2018 (Actual)
Study Completion Date: February 2018 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This was a double-blind, randomized, placebo-controlled, parallel-group, non-confirmatory study to assess the safety, tolerability, pharmacokinetics (PK), immunogenicity, pharmacodynamics and clinical efficacy of VAY736 administered intravenously as a single dose in 27 primary Sjögren's syndrome patients. Patients that received placebo treatment were offered open-label single dose iv VAY736 treatment at the end of the double-blind period.

Centers

Germany(1)

Objectives:

Primary objectives:

- 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)

Secondary objectives:

- To evaluate the effect of a single iv dose VAY736 versus placebo on self-reported outcomes in pSS patients at 12 weeks compared to Baseline as measured by the EULAR Sjögren's Syndrome Patient Reported Intensity (ESSPRI), the Short Form (36) Health Survey (SF-36) and the Multidimensional Fatigue Inventory (MFI) Questionnaire.
- To determine the changes in the physician global assessment of the patient's overall disease activity between Baseline and Week 12 as recorded by a visual analog scale (VAS)
- To determine the changes in the patients global assessment of their disease activity between Baseline and Week 12 as recorded by a VAS

- To determine the PK following a single dose iv VAY736 in pSS patients

Test Product (s), Dose(s), and Mode(s) of Administration

The investigational drug VAY736 150 mg lyophilisate in vials were packed by Novartis and supplied to the Investigator as open-labeled bulk medication.

Statistical Methods

Analysis of the primary variable:
The primary efficacy variable was the change from baseline in ESSDAI at Week 12, assumed to be normally distributed. The two active doses were pooled for the primary efficacy analysis, against the predefined dual efficacy criteria: statistically significant more reduction in ESSDAI with VAY736 treatment than placebo and also moderate confidence that the difference is at least 5 points or more in favor of VAY736. The statistical model was a repeated measures model, fitting terms for treatment by time point and baseline ESSDAI by time point, using PROC MCMC in SAS 9.4. The estimates of the difference between VAY736 and placebo at each time point were derived from this model and presented together with 95% credible intervals. The estimates of the posterior probabilities of the efficacy criteria being met were provided.
Analysis of the secondary variables:
Efficacy: The secondary efficacy variables were analyzed using a repeated measures model with treatment, the interaction between time and treatment (all as fixed effects) and baseline as a covariate and used a frequentist rather than a Bayesian approach.
Safety: All vital signs, ECG and laboratory data, including pregnancy tests data were listed by treatment, patient, and visit/time and abnormalities were flagged. Summary statistics were provided by treatment and visit/time. The number and percentage of patients with at least one AE were tabulated by body system and preferred term with a breakdown by treatment.
Pharmacokinetics: VAY736 plasma concentration data were listed by treatment, patient, and visit/sampling time point. Descriptive summary statistics were provided by treatment and visit/sampling time point.

Study Population: Key Inclusion/Exclusion Criteria

INCLUSION CRITERIA:
- Fulfilled revised European US consensus criteria for pSS
- ESSDAI value ≥ 6
- Elevated serum titers at screening of ANA (≥ 1:160)
- Seropositive at screening for anti-SSA and/or anti-SSB antibodies
- Stimulated whole salivary flow rate at screening of > 0 mL/min

EXCLUSION CRITERIA:
- Prior or previous use of (specific dosages and intervals prior to study start may apply):
B-cell depleting therapy (e.g., rituximab), Prednisone, anti-BAFF mAb, CTLA4-Fc Ig (abatacept), anti-TNF-α mAb, cyclophosphamide, azathioprine and medications known to cause dry mouth.
Hydroxychloroquine or methotrexate in a consistent dose for ≥ 3 months prior to randomization is allowed
- Active or recent history of clinically significant infection
- Vaccination within 2 month prior to study
- History of primary or secondary immunodeficiency

Participant Flow Table

Core Study

	Placebo	VAY736 3 mg/kg	VAY736 10 mg/kg
Started	6	12	9
Safety analysis set	9	6	12
PK analysis set	5[1]	6	12
PD (Pharmacodynamics) analysis set	9	6	12
Completed	5	10	9
Not Completed	1	2	0

Administrative problems	0	1	2

[1] for patients entering open label VAY736 10 mg/kg at Week 24

Open Label VAY736 10 mg/kg Extension

	Placebo	VAY736 3 mg/kg	VAY736 10 mg/kg
Started	5[1]	0[2]	0[2]
Completed	4	0	0
Not Completed	1	0	0
Administrative problems	1	0	0

[1] Patients received single dose of VAY736 10mg/kg at Week 24.
[2] Only patients origianally randomized to Placebo were allowed to enter this Period.

Baseline Characteristics

	Placebo	VAY736 3 mg/kg	VAY736 10 mg/kg	Total
Number of Participants [units: participants]	9	6	12	27
Age Continuous (units: Years) Mean ± Standard Deviation				
	46.7±11.29	46.8±8.75	55.3±13.35	50.5±12.16
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)				
Female	7	5	11	23
Male	2	1	1	4

Race/Ethnicity, Customized (units: Participants)				
Caucasian	9	6	12	27

Summary of Efficacy

Primary Outcome Result(s)

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

	Placebo	VAY736 3 mg/kg	VAY736 10 mg/kg	VAY736 Combined
Number of Participants Analyzed [units: participants]	9	6	12	18
Change in EULAR Sjögren's syndrome disease activity index (ESSDAI) (units: Points) 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 Analysis

Groups	Placebo, VAY736 Combined	Per protocol the primary analysis was between placebo and the combined VAY736 groups at Week 12.
P Value	0.678	

Method	Other repeated measures Bayesian analysis	with baseline as a covariate
Mean Difference (Final Values)	-0.93	
Standard Deviation	2.058	
95 % Confidence Interval 2-Sided	-5.007 to 3.180	

Overall incidence of Adverse Events

	Placebo	VAY736 3 mg/kg	VAY736 10 mg/kg	VAY736 Combined
Number of Participants Analyzed [units: participants]	9	6	12	18
Overall incidence of Adverse Events (units: Participants) Count of Participants (Not Applicable)				
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

Secondary Outcome Result(s)

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

	Placebo	VAY736 3 mg/kg	VAY736 10 mg/kg
Number of Participants Analyzed [units: participants]	9	6	12
Change in EULAR Sjögren's Syndrome Patient Response Index (ESSPRI) (units: Points) 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

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

	Placebo	VAY736 3 mg/kg	VAY736 10 mg/kg
Number of Participants Analyzed [units: participants]	9	6	12
Change in Short Form (36) Health Survey (SF-36) (units: Points) 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

Change in Multidimensional Fatigue Inventory (MFI)

	Placebo	VAY736 3 mg/kg	VAY736 10 mg/kg
Number of Participants Analyzed [units: participants]	9	6	12
Change in Multidimensional Fatigue Inventory (MFI) (units: Points) 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

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

	Placebo	VAY736 3 mg/kg	VAY736 10 mg/kg
Number of Participants Analyzed [units: participants]	9	6	12
Change in the physician's global assessment by means of Visual Analog Scale (VAS) (units: Points) 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

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

	Placebo	VAY736 3 mg/kg	VAY736 10 mg/kg
Number of Participants Analyzed [units: participants]	9	6	12
Change in the patient's global assessment by means of Visual Analog Scale (VAS)			

(units: Points) 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

VAY736 serum concentration - AUCinf

	VAY736 3 mg/kg	VAY736 10 mg/kg	Open label VAY736
Number of Participants Analyzed [units: participants]	6	12	5
VAY736 serum concentration - AUCinf (units: day*ug/mL) Median (Full Range)			
	389 (186 to 457)	1140 (515 to 1610)	971 (849 to 1340)

VAY736 serum concentration - AUClast

	VAY736 3 mg/kg	VAY736 10 mg/kg	Open label VAY736
Number of Participants Analyzed [units: participants]	6	12	5
VAY736 serum concentration - AUClast (units: day*ug/mL) Median (Full Range)			
	385 (184 to 457)	1140 (514 to 1610)	971 (848 to 1340)

VAY736 serum concentration - CL

	VAY736 3 mg/kg	VAY736 10 mg/kg	Open label VAY736
Number of Participants Analyzed [units: participants]	6	12	5
VAY736 serum concentration - CL (units: L/day) Median (Full Range)			
	0.594 (0.427 to 0.844)	0.584 (0.550 to 1.30)	0.686 (0.427 to 0.750)

VAY736 serum concentration - Cmax

	VAY736 3 mg/kg	VAY736 10 mg/kg	Open label VAY736
Number of Participants Analyzed [units: participants]	6	12	5
VAY736 serum concentration - Cmax (units: ug/mL) Median (Full Range)			
	65.0 (45.4 to 76.5)	213 (150 to 283)	205 (174 to 217)

VAY736 serum concentration - T1/2

	VAY736 3 mg/kg	VAY736 10 mg/kg	Open label VAY736

Number of Participants Analyzed [units: participants]	6	12	5
VAY736 serum concentration - T1/2 (units: days) Median (Full Range)			
	8.43 (6.99 to 13.8)	9.51 (5.38 to 15.2)	11.0 (4.94 to 17.4)

VAY736 serum concentration - Tmax

	VAY736 3 mg/kg	VAY736 10 mg/kg	Open label VAY736
Number of Participants Analyzed [units: participants]	6	12	5
VAY736 serum concentration - Tmax (units: hours) Median (Full Range)			
	2.03 (2.00 to 2.20)	2.03 (2.00 to 2.30)	2.10 (2.02 to 2.17)

VAY736 serum concentration - Vz

	VAY736 3 mg/kg	VAY736 10 mg/kg	Open label VAY736
Number of Participants Analyzed [units: participants]	6	12	5
VAY736 serum concentration - Vz (units: L) Median (Full Range)			

7.83 (6.55 to 10.7)	8.68 (7.15 to 12.4)	10.3 (4.93 to 18.6)

Summary of Safety

Safety Results

All-Cause Mortality

	Placebo N = 9	VAY736 3mg/kg N = 6	VAY736 10mg/kg N = 12	Open label VAY736 10mg/kg N = 5
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse Events (AEs) are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All AEs reported in this record are from date subject has provided informed consent until end of study (Week 28 or when B cell recovery was demonstrated).
Additional Description	All AEs were reported until week 52. After week 52 only AEs related to VAY736 and AEs related to infection, potential malignant events and neutropenia were recorded.
Source Vocabulary for Table Default	MedDRA (20.1)
Assessment Type for Table Default	Systematic Assessment

	Placebo N = 9	VAY736 3mg/kg N = 6	VAY736 10mg/kg N = 12	Open label VAY736 10mg/kg N = 5
Total participants affected	1 (11.11%)	2 (33.33%)	0 (0.00%)	1 (20.00%)
Gastrointestinal disorders				
Colitis	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Inguinal hernia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)
Infections and infestations				
Appendicitis	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications				
Jaw fracture	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Reproductive system and breast disorders				
Ovarian cyst torsion	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	Adverse Events (AEs) are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All AEs reported in this record are from date subject has provided informed consent until end of study (Week 28 or when B cell recovery was demonstrated).
Additional Description	All AEs were reported until week 52. After week 52 only AEs related to VAY736 and AEs related to infection, potential malignant events and neutropenia were recorded.
Source Vocabulary for Table Default	MedDRA (20.1)
Assessment Type for Table Default	Systematic Assessment

Frequent Event Reporting Threshold 5%

	Placebo N = 9	VAY736 3mg/kg N = 6	VAY736 10mg/kg N = 12	Open label VAY736 10mg/kg N = 5
Total participants affected	9 (100.00%)	6 (100.00%)	11 (91.67%)	5 (100.00%)
Blood and lymphatic system disorders				
Iron deficiency anaemia	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)
Cardiac disorders				
Palpitations	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)
Eye disorders				
Chalazion	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Keratitis	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Vitreous detachment	1 (11.11%)	0 (0.00%)	0 (0.00%)	1 (20.00%)
Gastrointestinal disorders				
Abdominal pain	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Auriculotemporal syndrome	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Noninfective sialoadenitis	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Toothache	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)
General disorders and administration site conditions				

Fatigue	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)
Non-cardiac chest pain	2 (22.22%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Immune system disorders				
Seasonal allergy	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Infections and infestations				
Bronchitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)
Conjunctivitis	0 (0.00%)	0 (0.00%)	1 (8.33%)	1 (20.00%)
Cystitis	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)
Gastroenteritis	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)
Gastrointestinal infection	1 (11.11%)	0 (0.00%)	1 (8.33%)	0 (0.00%)
Influenza	0 (0.00%)	1 (16.67%)	1 (8.33%)	0 (0.00%)
Nasopharyngitis	2 (22.22%)	5 (83.33%)	4 (33.33%)	5 (100.00%)
Oral herpes	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Otitis media	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (20.00%)
Sinusitis	1 (11.11%)	0 (0.00%)	1 (8.33%)	0 (0.00%)
Tooth infection	1 (11.11%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Urogenital infection bacterial	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications				
Infusion related reaction	1 (11.11%)	6 (100.00%)	9 (75.00%)	3 (60.00%)
Ligament rupture	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Limb injury	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Musculoskeletal and connective tissue disorders				

Arthralgia	0 (0.00%)	2 (33.33%)	0 (0.00%)	0 (0.00%)
Back pain	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)
Musculoskeletal pain	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Myalgia	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)
Rotator cuff syndrome	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Sjogren's syndrome	1 (11.11%)	1 (16.67%)	0 (0.00%)	1 (20.00%)
Synovitis	1 (11.11%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Nervous system disorders				
Dizziness	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)
Headache	3 (33.33%)	2 (33.33%)	2 (16.67%)	1 (20.00%)
Psychiatric disorders				
Insomnia	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Reproductive system and breast disorders				
Postmenopausal haemorrhage	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders				
Oropharyngeal pain	1 (11.11%)	1 (16.67%)	0 (0.00%)	1 (20.00%)
Skin and subcutaneous tissue disorders				
Photosensitivity reaction	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rash	1 (11.11%)	0 (0.00%)	1 (8.33%)	0 (0.00%)
Vascular disorders				
Hypotension	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)

Other Relevant Findings

None.

Conclusion:

VAY736 was safe and well-tolerated with mild-to-moderate, infusion-related reactions being observed in most of the patients receiving the investigational drug at both dose levels studied.
The pre-defined efficacy criteria for the difference between VAY736 and placebo treatment in the primary endpoint, ESSDAI (EULAR Sjögren's Syndrome Disease Activity Index), at Week 12 was not met. However, the outcome of the ESSDAI and secondary endpoints (EULAR Sjögren's Syndrome Patient Reported Index, Short Form (36) Health Survey, Multidimensional Fatigue Inventory, patient and physician global visual analog scale assessments) showed consistent trend towards clinical improvement to support a positive therapeutic effect with VAY736 compared to placebo.
The overall results in this single dose study in primary Sjögren's syndrome patients suggest potent and sustained B cell depletion by VAY736, which could lead to positive therapeutic effects in primary Sjögren's syndrome patients without major safety issues.
Moreover, a number of clinical endpoints (ESSDAI, EULAR Sjögren's Syndrome Patient Reported Index, Multidimensional Fatigue Inventory components and physician global assessment) persisted through to the end of study when B cell recovery criteria met and no further pharmacodynamic of the compound remained, suggesting potential for long term disease modification with VAY736 treatment of the primary Sjögren's syndrome disease process.

Date of Clinical Trial Report

31-Jul-2018