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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Ianalumab

Trial Indication(s)

Idiopathic Pulmonary Fibrosis

Protocol Number

CVAY736X2207

Protocol Title

A subject-, investigator-, and sponsor-blinded, randomized, placebo-controlled, multicenter study to investigate efficacy, safety, and tolerability of VAY736 in patients with idiopathic pulmonary fibrosis

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: December 20, 2017 (Actual)
Primary Completion Date: November 25, 2020 (Actual)
Study Completion Date: February 14, 2022 (Actual)

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Reason for Termination (If applicable)

The review of the results of an unplanned interim analysis (IA) led to a decision to stop dosing on 14-Dec-2020. Twenty-seven participants provided data for analysis at the unplanned IA. Fifteen had completed their treatment epoch. The decision was based on the results of the unplanned IA showing no sufficient evidence of clinical benefit. The decision to stop dosing was not due to any safety concerns.

Study Design/Methodology

This was an exploratory (non-confirmatory) randomized, participant-, investigator-, sponsor- blinded, placebo controlled study of VAY736 in idiopathic pulmonary fibrosis (IPF) patients. This study investigated the safety and efficacy of 300 mg VAY736 administered subcutaneously (s.c.) every 4 weeks for 48 weeks.

Participants were randomized in a 1:1 ratio on top of local standard of care (SOC), to receive VAY736 or placebo. Randomized subjects participated in a 48-week treatment epoch, followed by two follow-up epochs: the PK/safety follow-up epoch and the PD/safety follow-up epoch. The PK/safety follow-up epoch lasted for 20 weeks. When the PK/safety follow-up epoch was completed, participants in the placebo arm were discharged from the study; but participants in the active arm (those who had received VAY736) continued into the PD/safety follow-up epoch. Participants in the PD/safety follow-up epoch were followed until B-cell recovery (in the peripheral blood), defined as: B cells >=50/µL or B cells >= 80% of baseline (whichever occurred first). If a participant had not recovered his/her B-cells after a period of 2 years from the last dose of VAY736, then this participant was discharged from the study.

Centers

16 centers in 6 countries: United States(7), Ireland(1), Italy(3), Germany(2), United Kingdom(2), Canada(1)

Objectives:

Primary Objective

- To assess the efficacy of VAY736 in participants with IPF by looking at the change from baseline to end-of-treatment (48 weeks of treatment) in forced vital capacity (FVC).

Secondary Objectives

- To assess the impact of VAY736 on safety
- To assess the impact of VAY736 on survival
- To assess the impact of VAY736 on progression-free survival (PFS)

- To assess the impact of VAY736 on disease progression
- To assess the impact of VAY736 on a Composite Endpoint
- To assess the impact of VAY736 on pulmonary physiology
- To assess the impact of VAY736 on exercise capacity
- To assess the impact of VAY736 on gas exchange
- To assess the immunogenicity of VAY736 in IPF patients
- To assess the pharmacokinetics of VAY736 after multiple s.c. doses in IPF patients

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

- VAY736: 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks
- Placebo: Placebo administered subcutaneously every 4 weeks for 48 weeks

Statistical Methods

Analysis of the primary endpoint:

The primary endpoint was the change from baseline in FVC (L) from baseline to end of treatment epoch (48 Weeks). The following hypothesis was tested for VAY736+standard of care versus placebo+ standard of care:

- H_0: There was no difference or worsening in change from baseline in FVC (L) from baseline to 48 Weeks of treatment between VAY736+ standard of care and placebo+ standard of care.
- H_1: There was an improvement in change from baseline in FVC (L) from baseline to 48 Weeks of treatment between VAY736+ standard of care and placebo+ standard of care.

Test was conducted at a one-sided 10% level and 2-sided 80% CI of the estimates was displayed. The primary variable, change from baseline in FVC (L) was analyzed using a Mixed Effects Model for Repeated Measures (MMRM) in the PD analysis set and considered all assessments collected during the treatment epoch.

Analysis of secondary endpoints

- Time to events analyses (restricted to treatment epoch): The Kaplan-Meier estimates of the percentage of participants with the event of interest in each treatment group, along with 80% two-sided confidence intervals using Greenwood's formula, were provided. The two treatment groups were compared using a one-sided log rank test at the 10% significance level. The hazard ratio and its associated 80% two-sided confidence interval were estimated based on a Cox regression model using treatment group as main factor.

- Pulmonary physiology, Exercise capacity and Gas exchange: The same MMRM model described for the primary endpoint was used in these analyses.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- Male and female 40 to 80 years of age inclusive
- A diagnosis of definite or probable IPF within 5 years of the screening visit
- Forced Vital Capacity (FVC) 40-90% predicted (inclusive)
- Diffusing Capacity of the Lungs (DLCO), corrected for hemoglobin, 25-79% predicted (inclusive)
- Forced Expiratory Volume in first second (FEV1)/FVC >70%
- Unlikely to die from cause other than IPF within the next 3 years, in the opinion of the investigator
- Unlikely to undergo lung transplantation during this trial

Exclusion Criteria:
- Emphysema > fibrosis on screening high-resolution computed tomography (must be confirmed by central reader)
- History of major organ, hematopoietic stem cell or bone marrow transplant
- Clinically diagnosed acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) or other significant clinical worsening within 3 months of randomization
- New York Heart Association (NYHA) class III/IV Congestive Heart Failure (CHF), Ejection Fraction (EF) <25%
- Current smoker
- Prior use of any B-cell depleting therapy (e.g., rituximab, ofatumumab, or other anti-CD20 mAb, anti-CD40, anti-CD19,anti-CD22 mAb, anti-CD52 mAb, or anti-BAFF mAb)

Participant Flow Table

Treatment Epoch

	VAY736	Placebo	Total
Arm/Group Description	Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	Participants received placebo administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	

Started	14	16	30
Treated[1]	13	16	29
Completed	6	12	18
Not Completed	8	4	12
Adverse Event	0	1	1
Study terminated by sponsor	2	2	4
Subject/Guardian decision	4	0	4
Discontinued early with reason "other" selected	1	1	2
Withdrawal by Subject	1	0	1

[1] 1 participant randomized in the VAY736 arm did not receive treatment as the patient withdrew consent before first dosing.

PK/safety follow-up epoch

	VAY736	Placebo	Total
Arm/Group Description	Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	Participants received placebo administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	
Started	7	13	20
Completed	7	13	20
Not Completed	0	0	0

PD/safety follow-up epoch

	VAY736	Placebo	Total
Arm/Group Description	Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for	Participants received placebo administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	

	48 weeks on top of current standard-of-care therapy		
Started	7	0	7
Completed	5	0	5
Not Completed	2	0	2
Lost to Follow-up	1	0	1
Subject/Guardian decision	1	0	1

Baseline Characteristics

	VAY736	**Placebo**	**Total**
Arm/Group Description	Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	Participants received placebo administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	
Number of Participants [units: participants]	13	16	29
Age Continuous (units: Years) Analysis Population Type: Participants Mean ± Standard Deviation			
	69.7±9.30	68.3±8.15	68.9±8.55
Sex: Female, Male (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
Female	1	1	2
Male	12	15	27

Race/Ethnicity, Customized (units: Participants) Analysis Population Type: Participants			
White	13	16	29

Summary of Efficacy

Primary Outcome Result(s)

Change from baseline to end of treatment epoch (48 weeks of treatment) in Forced Vital Capacity (FVC)

Description	FVC was defined as the maximum amount of air that an individual was able to forcibly exhale from his / her lungs after taking the deepest breath they could. Change from baseline to end of treatment epoch (48 weeks of treatment) in Forced Vital Capacity (FVC) was analyzed using a Mixed Effects Model for Repeated Measures (MMRM) and considering all assessments collected during the treatment epoch. The model included treatment and visit as fixed effects, standard of care treatment (Nintedanib, Pirfenidone, or no treatment) as factor and baseline value as a covariate, treatment-by-visit and baseline-by-visit as interaction terms. A positive change from baseline indicates improvement. Baseline was defined as the last available assessment pre-dose before or on randomization date.
Time Frame	From baseline up to 48 weeks post first dose of study treatment

	VAY736	**Placebo**
Arm/Group Description	Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	Participants received placebo administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy
Number of Participants Analyzed [units: participants]	3	7
Change from baseline to end of treatment epoch (48 weeks of treatment) in Forced Vital Capacity (FVC). (units: Liter (L))	**Least Squares Mean ± Standard Error**	**Least Squares Mean ± Standard Error**
48 weeks of treatment	0.039 ± 0.1116	-0.023 ± 0.0773

Statistical Analysis

Groups	VAY736, Placebo	
Non-Inferiority/Equivalence Test	Superiority	
P Value	0.3248	1-sided p-values were obtained using MMRM Model
Method	Other: MMRM	
Other Least Squares Mean Difference	0.063	
Standard Error of the mean	0.1379	
80 % Confidence Interval 2-Sided	-0.115 to 0.241	

Secondary Outcome Result(s)

Percentage of participants with all-cause mortality events

Description	All-cause mortality events were defined as deaths due to any cause. Kaplan-Meier estimates of the percentage of participants with the event of interest along with 80% two-sided confidence intervals using Greenwood's formula are provided.
Time Frame	Up to 48 weeks post first dose of study treatment

	VAY736	**Placebo**

Arm/Group Description	Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	Participants received placebo administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy
Number of Participants Analyzed [units: participants]	12	16
Percentage of participants with all-cause mortality events (units: Percentage of participants)	**Number (80% Confidence Interval)**	**Number (80% Confidence Interval)**
	8.3 (2.39 to 26.92)	0 (NA to NA)[1]

[1] NA: Not estimable because no events occurred within this group

Statistical Analysis

Groups	VAY736, Placebo
Non-Inferiority/Equivalence Test	Other
P Value	0.868
Method	Log Rank

Percentage of participants with survival Idiopathic Pulmonary Fibrosis (IPF) -related mortality events

Description	IPF-related mortality events were defined as deaths due to IPF related cause. Kaplan-Meier estimates of the percentage of participants with the event of interest along with 80% two-sided confidence intervals using Greenwood's formula are provided.
Time Frame	Up to 48 weeks post first dose of study treatment

	VAY736	Placebo
Arm/Group Description	Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	Participants received placebo administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy
Number of Participants Analyzed [units: participants]	12	16
Percentage of participants with survival Idiopathic Pulmonary Fibrosis (IPF) -related mortality events (units: Percentage of participants)	**Number (80% Confidence Interval)**	**Number (80% Confidence Interval)**
	0 (NA to NA)[1]	0 (NA to NA)[1]

[1] NA: Not estimable because no events occurred within this group

Percentage of participants with Progression-free survival (PFS) events

Description: PFS events were divided into: 1) PFS1 events including progression (relative reduction in FVC ≥ 10%) or death due to all causes, and 2) PFS2 events including progression (relative reduction in FVC ≥ 10%) or death due to IPF-related causes. Kaplan-Meier estimates of the percentage of participants with the event of interest (PFS1 events or PFS2 events) along with 80% two-sided confidence intervals using Greenwood's formula are provided.

Time Frame: Up to 48 weeks post first dose of study treatment

	VAY736	Placebo
Arm/Group Description	Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	Participants received placebo administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy
Number of Participants Analyzed [units: participants]	12	16
Percentage of participants with Progression-free survival (PFS) events (units: Percentage of participants)	**Number (80% Confidence Interval)**	**Number (80% Confidence Interval)**

PFS1		61.0 (38.22 to 84.20)	31.9 (18.04 to 52.51)
PFS2		57.1 (33.44 to 82.83)	31.9 (18.04 to 52.51)

Statistical Analysis

Groups	VAY736, Placebo	PFS1
Non-Inferiority/Equivalence Test	Other	
P Value	0.921	
Method	Log Rank	
Hazard Ratio (HR)	2.6	
80 % Confidence Interval 2-Sided	1.1 to 6.3	

Statistical Analysis

Groups	VAY736, Placebo	PFS2
Non-Inferiority/Equivalence Test	Other	
P Value	0.863	
Method	Log Rank	

Hazard Ratio (HR)	2.2
80 % Confidence Interval 2-Sided	0.9 to 5.6

Percentage of participants with disease progression events

Description	The following disease progression events were considered: a) relative reduction in FVC ≥ 10%; b) relative reduction in Diffusing Capacity of the Lungs (DLCO) ≥ 15%; c) absolute reduction in Six Minute Walk Distance (6MWD) ≥ 50 m. Kaplan-Meier estimates of the percentage of participants with the event of interest along with 80% two-sided confidence intervals using Greenwood's formula are provided.
Time Frame	Up to 48 weeks post first dose of study treatment

	VAY736	**Placebo**
Arm/Group Description	Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	Participants received placebo administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy
Number of Participants Analyzed [units: participants]	12	16
Percentage of participants with disease progression events (units: Percentage of participants)	**Number (80% Confidence Interval)**	**Number (80% Confidence Interval)**
FVC	57.1 (33.44 to 82.86)	31.9 (18.04 to 52.51)
DLCO	73.8 (46.56 to 94.24)	56.1 (38.65 to 75.10)
6MWD	38.3 (19.96 to 64.88)	75.0 (58.52 to 88.74)

Statistical Analysis

Groups	VAY736, Placebo	FVC	

Non-Inferiority/Equivalence Test	Other
P Value	0.863
Method	Log Rank
Hazard Ratio (HR)	2.2
80 % Confidence Interval 2-Sided	0.9 to 5.6

Statistical Analysis

Groups	VAY736, Placebo	DLCO
Non-Inferiority/Equivalence Test	Other	
P Value	0.457	
Method	Log Rank	
Hazard Ratio (HR)	0.9	
80 % Confidence Interval 2-Sided	0.4 to 2.0	

Statistical Analysis

Groups	VAY736, Placebo	6MWD

Non-Inferiority/Equivalence Test	Other
P Value	0.019
Method	Log Rank
Hazard Ratio (HR)	0.3
80 % Confidence Interval 2-Sided	0.1 to 0.6

Percentage of participants with composite events

Description: Composite events were defined as: 1) death (all-cause mortality), or relative reduction in FVC ≥ 10%, or relative reduction in DLCO ≥ 15%, or relative reduction in 6MWD ≥ 50 m (composite endpoint 1); and 2) Death (IPF-related mortality), or relative reduction in FVC ≥ 10%, or relative reduction in DLCO ≥ 15%, or relative reduction in 6MWD ≥ 50 m (composite endpoint 2). Kaplan-Meier estimates of the percentage of participants with the event of interest along with 80% two-sided confidence intervals using Greenwood's formula are provided.

Time Frame: Up to 48 weeks post first dose of study treatment

	VAY736	**Placebo**
Arm/Group Description	Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	Participants received placebo administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy
Number of Participants Analyzed [units: participants]	12	16
Percentage of participants with composite events (units: Percentage of participants)	**Number** **(80% Confidence Interval)**	**Number** **(80% Confidence Interval)**
Composite Endpoint 1	81.0 (63.86 to 93.29)	66.3 (50.84 to 81.18)

Composite Endpoint 2	79.2 (61.07 to 92.70)	66.3 (50.84 to 81.18)

Statistical Analysis

Groups	VAY736, Placebo	Composite endpoint 1
Non-Inferiority/Equivalence Test	Other	
P Value	0.611	
Method	Log Rank	
Hazard Ratio (HR)	1.1	
80 % Confidence Interval 2-Sided	0.6 to 2.0	

Statistical Analysis

Groups	VAY736, Placebo	Composite endpoint 2
Non-Inferiority/Equivalence Test	Other	
P Value	0.549	
Method	Log Rank	
Hazard Ratio (HR)	1.1	

80 % Confidence Interval 2-Sided	0.6 to 1.9

Change from baseline to end of treatment epoch (48 weeks of treatment) in Diffusing Capacity of the Lungs

Description	DLCO is a measurement to assess the lungs' ability to transfer gas from inspired air to the bloodstream. DLCO was determined according to ATS guidelines. Change from baseline to end of treatment epoch (48 weeks of treatment) in diffusing capacity of the lung for carbon monoxide (DLCO) was analyzed using a Mixed Effects Model for Repeated Measures (MMRM) and considering all assessments collected during the treatment epoch. The model included treatment and visit as fixed effects, standard of care treatment (Nintedanib, Pirfenidone, or no treatment) as factor and baseline value as a covariate, treatment-by-visit and baseline-by-visit as interaction terms. A positive change from baseline indicates improvement. Baseline was defined as the last available assessment pre-dose before or on randomization date.
Time Frame	From baseline up to 48 weeks post first dose of study treatment

	VAY736	**Placebo**
Arm/Group Description	Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	Participants received placebo administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy
Number of Participants Analyzed [units: participants]	3	7
Change from baseline to end of treatment epoch (48 weeks of treatment) in Diffusing Capacity of the Lungs (units: milliliter/minute/millimeter Mercury)	**Least Squares Mean ± Standard Error**	**Least Squares Mean ± Standard Error**
48 weeks of treatment	-1.954 ± 1.0816	-1.033 ± 0.7244

Statistical Analysis

Groups	VAY736, Placebo
Non-Inferiority/Equivalence Test	Superiority

P Value	0.7576	1-sided p-values were obtained using MMRM Model
Method	Other: MMRM	
Other Least Squares Mean Difference	-0.920	
Standard Error of the mean	1.3109	
80 % Confidence Interval 2-Sided	-2.615 to 0.774	

Change from baseline to the end of treatment epoch (48 weeks of treatment) in 6-minute walk distance (6MWD)

Description: A standardized 6-minute walk test (6MWT) was performed in accordance with the guidelines of the American Thoracic Society 2002. The distance walked in six minutes (6MWD) was recorded. Change from baseline to end of treatment epoch (48 weeks of treatment) in 6MWD was analyzed using a Mixed Effects Model for Repeated Measures (MMRM) and considering all assessments collected during the treatment epoch. The model included treatment and visit as fixed effects, standard of care treatment (Nintedanib, Pirfenidone, or no treatment) as factor and baseline value as a covariate, treatment-by-visit and baseline-by-visit as interaction terms. A positive change from baseline indicates improvement. Baseline was defined as the last available assessment pre-dose before or on randomization date.

Time Frame: From baseline up to 48 weeks post first dose of study treatment

	VAY736	**Placebo**
Arm/Group Description	Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	Participants received placebo administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy
Number of Participants Analyzed [units: participants]	2	7
Change from baseline to the end of treatment epoch (48 weeks of treatment) in 6-minute walk distance (6MWD) (units: Meter (m))	**Least Squares Mean ± Standard Error**	**Least Squares Mean ± Standard Error**

After 48 weeks of treatment	19.743 ± 53.5268	-12.479 ± 28.9400

Statistical Analysis

Groups	VAY736, Placebo	
Non-Inferiority/Equivalence Test	Superiority	
P Value	0.3018	1-sided p-values were obtained using MMRM Model
Method	Other: MMRM	
Other Least Squares Mean Difference	32.222	
Standard Error of the mean	61.8632	
80 % Confidence Interval 2-Sided	-47.572 to 112.015	

Change from baseline to the end of treatment epoch (48 weeks of treatment) in distance saturation product

Description	Distance saturation product is the product of distance walked and lowest oxygen saturation during the 6-min walk test. Change from baseline to end of treatment epoch (48 weeks of treatment) in distance saturation product was analyzed using a Mixed Effects Model for Repeated Measures (MMRM) and considering all assessments collected during the treatment epoch. The model included treatment and visit as fixed effects, standard of care treatment (Nintedanib, Pirfenidone, or no treatment) as factor and baseline value as a covariate, treatment-by-visit and baseline-by-visit as interaction terms. A positive change from baseline indicates improvement. Baseline was defined as the last available assessment pre-dose before or on randomization date.
Time Frame	From baseline up to 48 weeks post first dose of study treatment

	VAY736	**Placebo**

Arm/Group Description	Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	Participants received placebo administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy
Number of Participants Analyzed [units: participants]	2	7
Change from baseline to the end of treatment epoch (48 weeks of treatment) in distance saturation product (units: Meter% (m%))	**Least Squares Mean ± Standard Error**	**Least Squares Mean ± Standard Error**
After 48 weeks of treatment	9.746 ± 52.2985	-19.420 ± 28.3755

Statistical Analysis

Groups	VAY736, Placebo	
Non-Inferiority/Equivalence Test	Superiority	
P Value	0.3140	1-sided p-values were obtained using MMRM Model
Method	Other: MMRM	
Other Least Squares Mean Difference	29.166	
Standard Error of the mean	60.0143	
80 % Confidence Interval 2-Sided	-48.220 to 106.553	

Change from baseline to the end of treatment epoch (48 weeks of treatment) in resting oxygen saturation level (on room air)

Description: Change from baseline to end of treatment epoch (48 weeks of treatment) in resting oxygen saturation (on room air) was analyzed using a Mixed Effects Model for Repeated Measures (MMRM) and considering all assessments collected during the treatment epoch. The model

included treatment and visit as fixed effects, standard of care treatment (Nintedanib, Pirfenidone, or no treatment) as factor and baseline value as a covariate, treatment-by-visit and baseline-by-visit as interaction terms. A positive change from baseline indicates improvement. Baseline was defined as the last available assessment pre-dose before or on randomization date.

Time Frame: From baseline up to 48 weeks post first dose of study treatment

	VAY736	Placebo
Arm/Group Description	Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	Participants received placebo administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy
Number of Participants Analyzed [units: participants]	5	7
Change from baseline to the end of treatment epoch (48 weeks of treatment) in resting oxygen saturation level (on room air) (units: Percentage (%))	**Least Squares Mean ± Standard Error**	**Least Squares Mean ± Standard Error**
After 48 weeks of treatment	-0.117 ± 1.0179	-1.887 ± 0.9415

Statistical Analysis

Groups	VAY736, Placebo	
Non-Inferiority/Equivalence Test	Superiority	
P Value	0.1269	1-sided p-values were obtained using MMRM Model
Method	Other: MMRM	
Other Least Squares Mean Difference	1.770	
Standard Error of the mean	1.5422	

80 % Confidence Interval 2-Sided	-0.219 to 3.759

Number of participants with positive serum anti-VAY736 antibodies

Description	Number of participants with positive serum anti-VAY736 antibodies. A bridging ELISA method that is designed to detect the presence of anti-VAY736 antibodies in human serum was used.
Time Frame	Day 1, 29, 85, 169, 253 and 337

	VAY736	Placebo
Arm/Group Description	Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	Participants received placebo administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy
Number of Participants Analyzed [units: participants]	10	15
Number of participants with positive serum anti-VAY736 antibodies (units: Participants)		
Day 1	1	3
Day 29	1	2
Day 85	1	1
Day 169	0	2
Day 253	2	1
Day 337	0	0

Ctrough of VAY736 from the serum concentration-time data

Description	The lowest serum concentration of VAY736 observed during a dosing interval at steady state (Ctrough) was determined
Time Frame	At pre-dose on Day 1, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309 and 337

	VAY736
Arm/Group Description	Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy
Number of Participants Analyzed [units: participants]	11
Ctrough of VAY736 from the serum concentration-time data (units: nanogram (ng) / mililiter (mL))	**Mean ± Standard Deviation**
Day 1	0.00 ± 0.000
Day 29	676.79 ± 499.931
Day 57	779.89 ± 645.363
Day 85	786.63 ± 501.225
Day 113	771.88 ± 623.268
Day 141	1316.05 ± 877.240
Day 169	1019.00 ± 587.097
Day 197	985.50 ± 495.652
Day 225	1271.10 ± 863.055
Day 253	998.57 ± 947.343
Day 281	705.00 ± 997.021
Day 309	827.40 ± 678.836
Day 337	688.50 ± 1172.124

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

Summary of Safety

Safety Results

Time Frame	From start up to end of study, assessed up to approximately 2.4 years
Additional Description	Safety analyses were performed in the safety set including all participants who received at least one dose of any study drug
Source Vocabulary for Table Default	MedDRA (25.0)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	VAY736 N = 13	**Placebo N = 16**	**Total N = 29**
Arm/Group Description	Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	Participants received placebo administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	Total
Total Number Affected	1	0	1
Total Number At Risk	13	16	29

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Serious Adverse Events

	VAY736 N = 13	Placebo N = 16	Total N = 29
Arm/Group Description	Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	Participants received placebo administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	Total
Total # Affected by any Serious Adverse Event	5	9	14
Total # at Risk by any Serious Adverse Event	13	16	29
Cardiac disorders			
Aortic valve incompetence	0 (0.00%)	1 (6.25%)	1 (3.45%)
Myocardial infarction	1 (7.69%)	1 (6.25%)	2 (6.90%)
Ear and labyrinth disorders			
Vertigo	0 (0.00%)	1 (6.25%)	1 (3.45%)
Eye disorders			
Retinal vein occlusion	0 (0.00%)	1 (6.25%)	1 (3.45%)
Gastrointestinal disorders			
Pancreatitis	1 (7.69%)	0 (0.00%)	1 (3.45%)
Infections and infestations			
Bronchitis	0 (0.00%)	1 (6.25%)	1 (3.45%)
Lower respiratory tract infection	0 (0.00%)	1 (6.25%)	1 (3.45%)
Pneumonia	0 (0.00%)	3 (18.75%)	3 (10.34%)
Metabolism and nutrition disorders			
Dehydration	0 (0.00%)	1 (6.25%)	1 (3.45%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma	1 (7.69%)	0 (0.00%)	1 (3.45%)
Prostate cancer	0 (0.00%)	1 (6.25%)	1 (3.45%)
Respiratory, thoracic and mediastinal disorders			
Hypoxia	1 (7.69%)	0 (0.00%)	1 (3.45%)
Idiopathic pulmonary fibrosis	1 (7.69%)	1 (6.25%)	2 (6.90%)
Vascular disorders			
Vasculitis	1 (7.69%)	0 (0.00%)	1 (3.45%)

Other (Not Including Serious) Adverse Events

	VAY736 N = 13	**Placebo N = 16**	**Total N = 29**
Arm/Group Description	Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	Participants received placebo administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy	Total
Total # Affected by any Other Adverse Event	13	15	28
Total # at Risk by any Other Adverse Event	13	16	29
Blood and lymphatic system disorders			
Anaemia	0 (0.00%)	1 (6.25%)	1 (3.45%)
Eosinophilia	0 (0.00%)	1 (6.25%)	1 (3.45%)
Cardiac disorders			

Aortic valve incompetence	0 (0.00%)	1 (6.25%)	1 (3.45%)
Arteriosclerosis coronary artery	0 (0.00%)	1 (6.25%)	1 (3.45%)
Palpitations	0 (0.00%)	1 (6.25%)	1 (3.45%)
Tachycardia	0 (0.00%)	1 (6.25%)	1 (3.45%)
Ear and labyrinth disorders			
Eustachian tube dysfunction	0 (0.00%)	1 (6.25%)	1 (3.45%)
Tinnitus	0 (0.00%)	1 (6.25%)	1 (3.45%)
Eye disorders			
Cataract	0 (0.00%)	1 (6.25%)	1 (3.45%)
Corneal degeneration	0 (0.00%)	1 (6.25%)	1 (3.45%)
Ocular hyperaemia	1 (7.69%)	0 (0.00%)	1 (3.45%)
Gastrointestinal disorders			
Abdominal pain	1 (7.69%)	0 (0.00%)	1 (3.45%)
Abdominal pain upper	0 (0.00%)	1 (6.25%)	1 (3.45%)
Diarrhoea	3 (23.08%)	1 (6.25%)	4 (13.79%)
Dyspepsia	2 (15.38%)	0 (0.00%)	2 (6.90%)
Enteritis	1 (7.69%)	0 (0.00%)	1 (3.45%)
Flatulence	1 (7.69%)	0 (0.00%)	1 (3.45%)
Frequent bowel movements	0 (0.00%)	1 (6.25%)	1 (3.45%)
Nausea	1 (7.69%)	2 (12.50%)	3 (10.34%)
Vomiting	1 (7.69%)	2 (12.50%)	3 (10.34%)
General disorders and administration site conditions			
Asthenia	0 (0.00%)	1 (6.25%)	1 (3.45%)
Chest discomfort	1 (7.69%)	0 (0.00%)	1 (3.45%)

Chest pain	1 (7.69%)	0 (0.00%)	1 (3.45%)
Fatigue	2 (15.38%)	1 (6.25%)	3 (10.34%)
Injection site bruising	1 (7.69%)	1 (6.25%)	2 (6.90%)
Injection site dermatitis	1 (7.69%)	0 (0.00%)	1 (3.45%)
Injection site erythema	2 (15.38%)	1 (6.25%)	3 (10.34%)
Injection site inflammation	1 (7.69%)	0 (0.00%)	1 (3.45%)
Injection site pain	0 (0.00%)	1 (6.25%)	1 (3.45%)
Injection site pruritus	3 (23.08%)	2 (12.50%)	5 (17.24%)
Injection site rash	1 (7.69%)	0 (0.00%)	1 (3.45%)
Injection site warmth	1 (7.69%)	0 (0.00%)	1 (3.45%)
Non-cardiac chest pain	0 (0.00%)	1 (6.25%)	1 (3.45%)
Immune system disorders			
Seasonal allergy	1 (7.69%)	0 (0.00%)	1 (3.45%)
Infections and infestations			
Bronchitis	2 (15.38%)	2 (12.50%)	4 (13.79%)
Conjunctivitis	0 (0.00%)	1 (6.25%)	1 (3.45%)
Influenza	1 (7.69%)	0 (0.00%)	1 (3.45%)
Lower respiratory tract infection	1 (7.69%)	1 (6.25%)	2 (6.90%)
Respiratory tract infection	2 (15.38%)	1 (6.25%)	3 (10.34%)
Rhinitis	0 (0.00%)	1 (6.25%)	1 (3.45%)
Tooth infection	0 (0.00%)	1 (6.25%)	1 (3.45%)
Upper respiratory tract infection	2 (15.38%)	2 (12.50%)	4 (13.79%)
Urinary tract infection	0 (0.00%)	1 (6.25%)	1 (3.45%)
Viral upper respiratory tract infection	1 (7.69%)	1 (6.25%)	2 (6.90%)

Injury, poisoning and procedural complications			
Contusion	1 (7.69%)	1 (6.25%)	2 (6.90%)
Facial bones fracture	1 (7.69%)	0 (0.00%)	1 (3.45%)
Heat stroke	0 (0.00%)	1 (6.25%)	1 (3.45%)
Injection related reaction	2 (15.38%)	0 (0.00%)	2 (6.90%)
Sunburn	0 (0.00%)	2 (12.50%)	2 (6.90%)
Investigations			
Alanine aminotransferase increased	2 (15.38%)	0 (0.00%)	2 (6.90%)
Antinuclear antibody increased	0 (0.00%)	1 (6.25%)	1 (3.45%)
Blood creatine phosphokinase decreased	1 (7.69%)	0 (0.00%)	1 (3.45%)
Blood creatinine increased	1 (7.69%)	0 (0.00%)	1 (3.45%)
Blood glucose increased	1 (7.69%)	0 (0.00%)	1 (3.45%)
Blood parathyroid hormone decreased	1 (7.69%)	0 (0.00%)	1 (3.45%)
Blood potassium increased	1 (7.69%)	0 (0.00%)	1 (3.45%)
Blood triglycerides increased	0 (0.00%)	1 (6.25%)	1 (3.45%)
Blood urea increased	1 (7.69%)	0 (0.00%)	1 (3.45%)
Blood urine present	1 (7.69%)	0 (0.00%)	1 (3.45%)
Escherichia test positive	0 (0.00%)	1 (6.25%)	1 (3.45%)
Gamma-glutamyltransferase increased	2 (15.38%)	0 (0.00%)	2 (6.90%)
Glucose urine present	0 (0.00%)	1 (6.25%)	1 (3.45%)
Hepatic enzyme increased	1 (7.69%)	0 (0.00%)	1 (3.45%)
Lymphocyte count decreased	1 (7.69%)	0 (0.00%)	1 (3.45%)
Mean cell volume increased	1 (7.69%)	0 (0.00%)	1 (3.45%)
Monocyte count increased	2 (15.38%)	0 (0.00%)	2 (6.90%)
Neutrophil count increased	1 (7.69%)	0 (0.00%)	1 (3.45%)

Protein urine present	0 (0.00%)	1 (6.25%)	1 (3.45%)
Urine albumin/creatinine ratio increased	0 (0.00%)	1 (6.25%)	1 (3.45%)
Urine analysis abnormal	1 (7.69%)	0 (0.00%)	1 (3.45%)
Urine protein/creatinine ratio increased	1 (7.69%)	1 (6.25%)	2 (6.90%)
Weight decreased	1 (7.69%)	4 (25.00%)	5 (17.24%)
White blood cell count increased	1 (7.69%)	0 (0.00%)	1 (3.45%)
Metabolism and nutrition disorders			
Decreased appetite	0 (0.00%)	1 (6.25%)	1 (3.45%)
Hyperkalaemia	1 (7.69%)	0 (0.00%)	1 (3.45%)
Vitamin D deficiency	1 (7.69%)	0 (0.00%)	1 (3.45%)
Musculoskeletal and connective tissue disorders			
Arthralgia	1 (7.69%)	0 (0.00%)	1 (3.45%)
Back pain	0 (0.00%)	1 (6.25%)	1 (3.45%)
Limb discomfort	0 (0.00%)	1 (6.25%)	1 (3.45%)
Muscle spasms	0 (0.00%)	1 (6.25%)	1 (3.45%)
Musculoskeletal pain	1 (7.69%)	0 (0.00%)	1 (3.45%)
Osteoporosis	0 (0.00%)	1 (6.25%)	1 (3.45%)
Pain in extremity	2 (15.38%)	0 (0.00%)	2 (6.90%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma	1 (7.69%)	0 (0.00%)	1 (3.45%)
Dysplastic naevus	0 (0.00%)	1 (6.25%)	1 (3.45%)
Keratoacanthoma	1 (7.69%)	0 (0.00%)	1 (3.45%)
Nervous system disorders			
Carotid artery stenosis	0 (0.00%)	1 (6.25%)	1 (3.45%)

Cervical radiculopathy	0 (0.00%)	1 (6.25%)	1 (3.45%)
Cognitive disorder	0 (0.00%)	1 (6.25%)	1 (3.45%)
Dizziness	0 (0.00%)	1 (6.25%)	1 (3.45%)
Headache	2 (15.38%)	2 (12.50%)	4 (13.79%)
Memory impairment	0 (0.00%)	1 (6.25%)	1 (3.45%)
Paraesthesia	1 (7.69%)	0 (0.00%)	1 (3.45%)
Tremor	0 (0.00%)	1 (6.25%)	1 (3.45%)
Psychiatric disorders			
Depression	0 (0.00%)	1 (6.25%)	1 (3.45%)
Insomnia	2 (15.38%)	1 (6.25%)	3 (10.34%)
Renal and urinary disorders			
Haematuria	0 (0.00%)	1 (6.25%)	1 (3.45%)
Pollakiuria	0 (0.00%)	1 (6.25%)	1 (3.45%)
Proteinuria	1 (7.69%)	0 (0.00%)	1 (3.45%)
Urinary incontinence	0 (0.00%)	1 (6.25%)	1 (3.45%)
Respiratory, thoracic and mediastinal disorders			
Cough	3 (23.08%)	1 (6.25%)	4 (13.79%)
Dysphonia	0 (0.00%)	1 (6.25%)	1 (3.45%)
Dyspnoea	1 (7.69%)	1 (6.25%)	2 (6.90%)
Epistaxis	0 (0.00%)	1 (6.25%)	1 (3.45%)
Hypoxia	0 (0.00%)	1 (6.25%)	1 (3.45%)
Idiopathic pulmonary fibrosis	1 (7.69%)	3 (18.75%)	4 (13.79%)
Nasal congestion	1 (7.69%)	1 (6.25%)	2 (6.90%)
Skin and subcutaneous tissue disorders			

Alopecia	0 (0.00%)	1 (6.25%)	1 (3.45%)
Dermatitis atopic	0 (0.00%)	1 (6.25%)	1 (3.45%)
Drug eruption	0 (0.00%)	1 (6.25%)	1 (3.45%)
Hyperhidrosis	1 (7.69%)	0 (0.00%)	1 (3.45%)
Keloid scar	1 (7.69%)	0 (0.00%)	1 (3.45%)
Photosensitivity reaction	0 (0.00%)	1 (6.25%)	1 (3.45%)
Pruritus	0 (0.00%)	1 (6.25%)	1 (3.45%)
Rash	0 (0.00%)	2 (12.50%)	2 (6.90%)
Rash erythematous	1 (7.69%)	0 (0.00%)	1 (3.45%)
Skin lesion	1 (7.69%)	0 (0.00%)	1 (3.45%)
Vascular disorders			
Hot flush	2 (15.38%)	0 (0.00%)	2 (6.90%)
Hypertension	1 (7.69%)	0 (0.00%)	1 (3.45%)

Other Relevant Findings

None

Conclusion

An unplanned IA was conducted. Twenty-seven patients provided data for analysis at the unplanned IA. Fifteen had completed their treatment epoch. The review of the results led to a decision to stop dosing on 14-Dec-2020. This decision was based on the unplanned IA showing no sufficient evidence of clinical benefit. The decision to stop dosing was not due to any safety concerns.

During the study, the majority of the participants experienced AEs (92.3% in VAY736 arm) and AEs were mostly mild in severity (76/94). There was a higher percentage of SAEs in the placebo arm compared with the VAY736 arm. There were

no AEs leading to treatment discontinuation in the VAY736 group. There were two fatal SAEs reported. One participant died in the screening period. The other fatality was due to disease progression (worsening IPF) occurring in a participant approximately 2 months after a single dose of active study treatment; this event was considered not related to the study treatment. The safety profile of VAY736 obtained in this Phase 2 trial did not reveal new safety signals and is consistent with the safety profile of other B-cell depleting agents.

In conclusion, VAY736 was safe and well-tolerated. However, no clinically relevant impact on disease progression was noted.

Date of Clinical Trial Report

13-Jan-2023