Study Results Synopsis for Public Disclosure

Name of product: VAY736 / Ianalumab

Protocol identification number: CVAY736J12101

EudraCT no. 2020-005881-32; EU CT no. 2024-511489-35-00

ClinicalTrials.gov no. NCT04903197

Title of study: A phase Ib, multi-center, open-label dose escalation and expansion platform study of VAY736 as single agent and in combination with select antineoplastic agents in patients with non-Hodgkin Lymphoma (NHL)

Study center(s): 10 centers in 7 countries- Australia (1), China (2), Japan (1), Singapore (1), Republic of Korea (2), Italy (2), Germany (1)

Publication (reference): None

Study period:

Study initiation date: 24-Jan-2022 (first patient first visit)

Early termination date: 24-Feb-2025 (last patient last visit)

Phase of development (phase of this clinical study): Ib

Objectives: The purpose of this synopsis was to provide results of the final analysis of the study. The primary and secondary objectives with the corresponding endpoints are provided in Table 2-1.

Due to the early termination of the study based on business decisions, this synopsis reports primary and secondary endpoints of the escalation part of the study only, with a data cut off of 24-Feb-2025.

Table 0-1 Objectives and related endpoints (all arms)

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
To characterize the safety and tolerability in patients with NHL and identify a maximum tolerated dose (MTD) and/or recommended dose (RD) for VAY736 single agent and in combination with partner therapies	Safety: Incidence and nature of dose limiting toxicities (DLTs) Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), changes in laboratory values, vital signs and electrocardiograms (ECGs) Tolerability: Dose interruptions, reductions and dose intensity
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
To evaluate preliminary anti-tumor activity of VAY736 single agent and in combination with partner therapies	Overall response rate (ORR) and best overall response (BOR) rate by Lugano Classification (fluorodeoxyglucose-positron emission tomography (FDG-PET) computerized tomography (CT) Scan)

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
To characterize the pharmacokinetics (PK) of VAY736 single agent and its combination partners	Serum/plasma concentrations and PK parameters of VAY736 and combination partners
To evaluate immunogenicity of VAY736 single agent and in combination with partner therapies	Change from baseline in anti-drug antibody (ADA)

Study design and methodology: This is a phase Ib, multi-center, open-label study with multiple treatment arms. The open platform design of this study was adaptive to facilitate the introduction and termination of combination candidates by protocol amendment. The treatment arms conducted in the study were as follows:

Arm 1A: VAY736 single agent dose escalation in diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL) and marginal-zone lymphoma (MZL)

Arm 2A: VAY736 and lenalidomide dose escalation in DLBCL, FL, MCL and MZL (As of 13-Jun-2023, enrollment has been halted in this combination arm based on business decision)

Enrollment of the study was halted for business reasons unrelated to safety on 29-Aug-2024 and was never resumed. As a result, the planned dose expansion part (Arm 1B and Arm 2B) was never initiated.

During the dose escalation part of each treatment arm/group, participants were treated with VAY736 alone or in combination with lenalidomide. Each enrolled participant underwent a screening period of 28 days, followed by a treatment period for those who satisfied all the inclusion criteria in screening, starting from Cycle 1 Day 1 (C1D1) which continued until the participant discontinued study treatment. After discontinuation, participants were followed up for safety for 180 days.

Diagnosis and main criteria for inclusion: The study population consisted of adult male and female participants diagnosed with relapsed or refractory (r/r) NHL, who have received and failed or were intolerant to standard of care therapy for their indication (at least two prior therapies/regimens, including an anti-CD20 therapy for NHL) and for whom there was no curative therapy.

The key inclusion and exclusion criteria pertaining to both treatment arms are provided below:

The key inclusion criteria were as follows:

- Adult participants with histologically confirmed diagnosis of B-cell NHL with all subtypes of Diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), and marginal zone lymphoma (MZL) per WHO 2016 criteria. Participants in subtype arms e.g. diffuse large B-cell lymphoma (DLBCL) must have confirmed diagnosis of r/r DLBCL.
- Received and failed or be intolerant to standard of care therapy (at least two prior lines, including an anti-CD20 therapy). Participants deemed in the judgement of the investigator as, not appropriate candidates for any other approved therapy with established benefit for the specific type of r/r NHL
- Must have measurable disease and ECOG ≤ 2

Key exclusion criteria:

- Baseline laboratory results outside of protocol defined ranges
- Primary central nervous system (CNS) lymphoma
- Ongoing immunosuppressive therapy for treatment of lymphoma
- History of hypersensitivity to VAY736 or any of its excipients or to drugs in similar chemical classes (e.g. mAb)
- Impaired cardiac function or clinically significant cardiac disease
- History of or current interstitial lung disease or pneumonitis ≥ grade 2
- Human immunodeficiency virus (HIV) infection
- Active hepatitis C infection and/or hepatitis B infection
- Pregnant or nursing (lactating) women
- Women of child-bearing potential unless they are using highly effective methods of contraception

Test and reference therapies, dose and mode of administration, batch number:

Participants in ARM 1A received VAY736 (150 mg/1 mL Liquid in vial) administered via i.v. infusion over 2 hours, once every 2 weeks (Day 1 and Day 15 of each cycle), at a dosing cycle of 28 days. In Arm 2A, VAY736 3mg/kg Q2W was given in combination with lenalidomide 20 mg once daily (QD).

Protocol amendments and other changes to study conduct:

This synopsis describes the conduct of the study according to the Protocol Amendment v06, which was the final protocol dated 19-Oct-2023. The study protocol was amended six times in total. The key features of each amendment are given in Table 2-3.

Table 0-2 Protocol amendments

Version and date	Summary of key changes
Version 6, 19-Oct-2023	The primary purpose of this protocol amendment was to incorporate the changes related to discontinuation of the combination Arm (VAY736 and lenalidomide) and not proceeding with Arm 3 (VAY736 + CC-99282) due to business reasons, which are not safety-related. As of this amendment, VAY736 and lenalidomide dose expansion (Arm 2B) and VAY736 + CC-99282 dose escalation and expansion (Arms 3A and B) were not open.
Version 5, 20-Mar-2023	The key purpose of this amendment was to add CC-99282, a novel Cereblon (CRBN) E3 Ligase Modulator (CELMoD) agent, as a new combination partner with VAY736 and to modify the requirements for eligibility and assessments to reduce the burden of non-critical assessments and facilitate enrollment of participants with rapidly progressive disease who are in urgent need of treatment. Additional changes were made in order to provide clarification on protocol aspects, including exclusion criteria, safety monitoring and assessments.

Version and date	Summary of key changes
Version 4, 30-Sep-2022	The primary purpose of this amendment was to incorporate requests from a Health Authority (HA), which asked to clarify that the provisional doses for VAY736 as a single agent and in combination were applicable to both the single agent arm and the combination arms. Also, in response to the feedback, the minimum group size was updated to at least 3 participants, if any participant experiences a DLT during the DLT period, or any participant experiences any Grade 2 adverse event (AE) or higher, unless the AE is clearly unrelated to VAY736. Based on an updated local guideline and safety data in the malignancy population (CLL data from CVAY736Y2102 study), the amendment also updated that hospitalization during escalation is only required through Cycle 1 Day 8 in Japan.
Version 3, 13-May-2022	This amendment was primarily made to incorporate the requests from a Health Authority (HA) to update the existing exception for dose limiting toxicity for platelet counts. Changes were made to include additional subtypes of relapsed or refractory (r/r) non-Hodgkin Lymphoma (NHL) in VAY736 single agent dose escalation. Disease relevant patient-reported outcomes (PROs) were added to dose expansion arms. The dose escalation arm of VAY736 in combination with lenalidomide was opened for enrollment at the planned doses of 3 mg/kg Q2W and 20 mg QD respectively.
Version 2, 29-Oct-2021	The primary purpose of this protocol amendment was to address Health Authority feedback regarding the eligibility criteria, starting dose of lenalidomide, discontinuation criteria and timing of live vaccinations after last dose. To incorporate this feedback, the inclusion criteria was modified to include only those participants judged by the investigator as unsuitable for any other approved therapy for their specific type of relapsed/refractory non-Hodgkin lymphoma. Also, the starting dose level of lenalidomide was revised from 25 mg to 20 mg QD PO for Days 1-21 of 28-day cycles for 12 cycles. Prohibition of live or attenuated vaccines was extended from the end of the treatment period to 14 months after the last dose of VAY736. The discontinuation criteria was updated to include disease progression as one of the criteria, unless it is due to clinical benefit.
Version 1, 18-May-2021	This amendment was made to address HA feedback regarding the eligibility criteria, DLT assessment, statistical considerations and assessments. The inclusion criteria for B cell NHL was updated to avoid inclusion of subtypes other than those listed. Further clarifications were made in eligibility criteria including updating of subtypes of DLBCL, renal function criteria, washout period for conventional chemotherapy changed from 4 weeks to 2 weeks and double hit or triple hit DLBCL in exclusion criteria. DLT definition and criteria were updated and assessment schedule of DLTs was changed to cycle 1. Certain statistical considerations were updated based on the HA feedback. Further clarifications on VAY736 infusion time, vital signs, observation period of at least 1 hour after the infusion, additional guidance for premedications, grade 3 or 4 infusion reactions and starting dose of VAY736 in lenalidomide arms were provided.

Clinical trial quality risk management: None

Criteria for evaluation:

Efficacy:

Efficacy was evaluated according to the Lugano classification 2014 for response assessment of non-Hodgkin lymphomas. Preliminary efficacy was assessed by the evaluation of response, evaluation of Best Overall Response (BOR) from the start of the treatment until disease progression/recurrence and duration of response (DOR).

Pharmacokinetics:

PK parameters such as AUClast, AUCinf, AUCtau, Cmax, Tmax, Lambda_z, T1/2, CL, and Vz were estimated and reported for VAY736. For lenalidomide, only PK exposure parameters (eg Cmax, Tmax, AUClast) were determined. Anti-drug antibodies (ADA) directed against VAY736 were assessed.

Safety:

Safety was monitored by assessing the following parameters:

- Physical examination
- Vital signs
- Height and weight
- ECOG performance status
- Laboratory evaluations including hematology, chemistry, urinalysis, coagulation, thyroid, virology testing, additional tests (e.g. FSH), pregnancy test, and immunology
- Chest X-ray (Japan only)
- Cardiac assessments – ECG
- Additional liver function tests and renal function tests- as appropriate
- Adverse events (AEs) and serious AEs (SAEs), including AEs leading to treatment discontinuation.
- Adverse event of special interest (AESI)

Statistical methods:

All analyses were performed by Novartis personnel. SAS version 9.4 was used to perform all data analyses and to generate tables, figures and listings. PK parameters were calculated using non-compartmental methods available in Phoenix WinNonlin.

All safety data, including laboratory measurements, vital signs, adverse events, ECG, were considered primary endpoints, for the dose escalation part of the study. Safety set was used for all safety analyses, with the exception of DLTs for which the Dose-Determining Set (DDS) was used. Best overall response (BOR) and overall response rate (ORR) were the secondary efficacy endpoints used to evaluate anti-tumor activity of VAY736 single agent and in combination with lenalidomide. The Pharmacokinetic Analysis Set (PAS) was used for all PK data analyses and PK summary statistics. PK parameters were determined using non-compartmental methods. Immunogenicity of VAY736 i.e. the incidence of anti-VAY736 antibodies (Anti-Drug Antibody (ADA)) was assessed by treatment arm/group.

The analysis sets were defined as follows:

Full Analysis Set (FAS)

The FAS comprised all participants who received at least one dose of study treatment (i.e. for the combination arm, at least one dose of VAY736 or lenalidomide). Participants were analyzed according to the study treatment received, defined as:

- the assigned treatment if the patient took at least one dose of that treatment, or
- the first treatment received if the assigned treatment was never received

Safety Analysis Set (SS)

Same as definition of FAS in this study

Dose Determining Set (DDS)

The DDS included all FAS participants treated in dose escalation who met the minimum exposure criterion and had sufficient safety evaluations as determined by Novartis and Investigators, or experienced a dose limiting toxicity (DLT) during the DLT-evaluation period (i.e. the first 28 days of dosing).

A patient has met the minimum exposure criterion if the participant received, during the DLT-evaluation period,

- all planned doses of VAY736 (2 for Q2W) for single agent, or
- all planned doses of VAY736 (2 for Q2W) and at least 75% (i.e. 16 days) of the planned doses of lenalidomide (QD, Day 1 to 21)

Pharmacokinetic Analysis Set (PAS)

The PAS includes all participants who satisfied all of the following conditions and were considered having evaluable PK profiles:

- having received one of the planned treatments
- having provided at least one primary PK parameter

Immunogenicity Prevalence Set (IGPS)

The IGPS includes all participants in the FAS with a determinant baseline IG sample **or** at least one determinant post-baseline IG sample.

Immunogenicity Incidence Set (IGIS)

The IGIS includes all participants in the IGPS with a determinant baseline immunogenicity (IG) sample and at least one determinant post-baseline IG sample. IGPS and IGIS are not applicable to lenalidomide.

From the EU EEA perspective, study CVAY736J12101 was transitioned to EU CT Regulation, EU CTR 536/2014, on 02Jul2024. Therefore, and since then, the study complied with the EU CTR safety reporting requirements, including those related to the additional treatment identified as AxMPs for the study as per EU CT Regulation definition.

Due to early termination of the study, only the primary and secondary endpoints of the escalation part of the study are reported in this synopsis. Bayesian Hierarchical Logistic Regression Model (BHLRM) was rerun post-dose escalation meeting (DEM) and before database lock (DBL) due to a change in DLT analysis output caused by incorrect DDS data,

which was identified and rectified before DBL. This was not a statistical analysis plan (SAP)-specified analysis. The correct output was reported in this synopsis.

Summary – Results

Demographic and background characteristics:

In total, 18 participants received study treatment, comprising 16 participants treated with VAY736 single agent in ARM 1A and 2 participants with VAY736 and lenalidomide in ARM 2A.

The median age of participants was 56.5 years (range: 33 – 82) and 73.5 years (range: 72 – 75) in ARM 1A and 2A, respectively. In ARM 1A, 13 participants (81.3%) were male. In ARM 2A, all participants were male.

Eleven participants (68.8%) and 1 participant (50.0%) in ARM 1A and 2A, respectively, were Asian. Five participants (31.3%) in ARM 1A and 1 participant (50.0%) in ARM 2A were White.

Ten participants (62.5%) in ARM 1A and 1 (50.0%) in ARM 2A had baseline ECOG performance status of 1.

Protocol deviations:

In ARM 1A, at least one protocol deviation was reported in 7 participants (43.8%), comprising 4 participants in the 3 mg/kg Q2W treatment group and 3 participants in the 12 mg/kg Q2W treatment group. One protocol deviation was reported in 1 participant (50.0%), in ARM 2A.

Exposure:

In ARM 1A, the mean (SD) duration of exposure (DOE) of participants treated with VAY736 3 mg/kg, 6 mg/kg and 12 mg/kg Q2W was 5.7 (6.95) months, 2.7 (1.28) months and 3.5 (2.22) months, respectively. In ARM 2A, the mean (SD) DOE to VAY736 was 1.1 (1.35) months. The mean (SD) DOE to lenalidomide was 1.0 (1.25) months.

Efficacy, pharmacokinetic, and immunogenicity results:

ARM 1A (VAY736 single agent)

- Partial Response (PR) was observed in 2 participants (40.0%) treated with 3 mg/kg Q2W. Stable Disease (SD) was reported in 1 participant (20.0%) treated with 6 mg/kg Q2W and in 3 participants (50.0%) with 12 mg/kg Q2W. ORR was 12.5% (90% CI: 2.3, 34.4).
- At Cycle 1 and Cycle 3, both Cmax and AUC0–336hr increased approximately proportionally with dose. T1/2 (geo-mean) was consistent across doses, ranging from 4.44 to 5.50 days at Cycle 1 Day 1, and ranging from 4.57 to 6.66 days at Cycle 3.
- No participant developed treatment-induced or treatment-boosted ADA during the study.

ARM 2A (VAY736 and lenalidomide)

- No response was observed.
- At C1D1, the geo-mean (geo-CV%) of AUC0–336h at C1D1 was 235 (69.9) day*µg/mL, Tmax (median) was 2.03 hours and the geo-mean (geo-CV%) Cmax was 83.9 (16.8) µg/mL. T1/2 at C1D1 was 5.32 days. There is no C3D1 data because neither participant received treatment beyond Cycle 2.

- No participant developed treatment-induced or treatment-boosted ADA during the study.

Safety results:

ARM 1A (VAY736 single agent)

- There was no DLT observed.
- The mean (SD) duration of exposure (DOE) of participants treated with VAY736 3 mg/kg, 6 mg/kg and 12 mg/kg Q2W was 5.7 (6.95) months, 2.7 (1.28) months and 3.5 (2.22) months, respectively.
- At least one AE suspected to be related to VAY736 was reported in 10 out of 16 participants (62.5%). AEs, suspected to be related to VAY736, reported in >10% participants included hypokalaemia (n=4, 25.0%), decreased neutrophil count, infusion related reaction (n=3 each, 18.8%), anaemia, increased alanine aminotransferase, increased aspartate aminotransferase, nausea, pneumonia, hypophosphatemia, decreased platelet count (n=2 each, 12.5%).
- Two participants (12.5%) respectively treated with 3 mg/kg Q2W and 6 mg/kg Q2W, experienced at least one grade ≥ 3 AE suspected to be related to VAY736. The former experienced grade ≥ 3 increased lipase that led to permanent discontinuation of study treatment.
- Five participants (31.3%) experienced at least 1 SAE of SARS-CoV-2 positivity, constipation, pyrexia, pneumonia, COVID-19 pneumonia (n=1 each, 6.3%).
- Most frequently reported adverse events of special interest (AESIs) included neutropenia and infections (n=6, 37.5%, each), and infusion related reaction (n=3, 18.8%). Grade ≥ 3 AESI included neutropenia (n=4, 25.0%), infections (n=2, 12.5%), and malignancy (n=1, 6.3%).
- Grade ≥ 3 hematological abnormalities decreased lymphocytes (n=4, 25.0%), decreased neutrophil count, decreased hemoglobin (n=3 each, 18.75%) and decreased leukocyte count (n=1, 6.25%).
- Three participants (18.8%) died respectively of intestinal perforation, COVID-19 pneumonia and respiratory failure due to SARS-CoV-2 positivity. VAY736 was assessed not to have a causality relationship with these deaths.

ARM 2A (VAY736 and lenalidomide)

- There was no DLT observed.
- The mean (SD) DOE to VAY736 was 1.1 (1.35) months. The mean (SD) DOE to lenalidomide was 1.0 (1.25) months.
- One participant (50.0%) experienced at least one Grade ≥3 AE of neutropenia and thrombocytopenia suspected to be related to study treatment. Neutropenia is classified as an AESI for VAY736.
- One (50.0%) participant experienced SAEs of atrial fibrillation, thrombocytopenia and hypoxia. The latter led to permanent study treatment discontinuation.
- Grade ≥ 3 hematological abnormalities included decreased lymphocytes (n=2, 100%), decreased neutrophil count and decreased leukocyte count (n=1 each, 50.0%). Both participants had decreased lymphocytes at baseline.

- No significant abnormal changes in clinical chemistry parameters from baseline were observed.
- Two participants (100.0%) died of disease progression of study indication.

Conclusions:

In this study, VAY736 was administered as a single agent or in combination with lenalidomide (as of Protocol amendment v06). The observed Cmax and AUCtau of VAY736 were approximately dose proportional when administered as single agent. No DLT was observed at the doses of VAY736 administered. Neither RD nor MTD could be declared because of early study termination. Proportionally more AEs suspected to be related to VAY736 single agent therapy was reported with increasing dose administered. However, the sample size of each treatment group and the absolute number of AEs reported were small. Therefore, a correlation between AE frequency and dosage of VAY736 administered could not be established.

With protocol amendment 6 dated 19-Oct-2023, lenalidomide became the only combination partner to have been co-administered with VAY736 in this study. However, only 2 participants were eventually treated with VAY736 3 mg/kg Q2W in combination with lenalidomide 20 mg QD. The DOE of study treatment was approximately 1 month and no response was observed. Because of the brevity of their therapy, it is not possible to draw conclusions on the combination's safety, PK and efficacy findings.

Overall, VAY736 was safe and tolerable when administered up to 12 mg/kg Q2W as single agent. Responses were observed when VAY736 was administered at 3 mg/kg Q2W to participants with advanced NHL.