NEW ZEALAND DATA SHEET

1. VENCLEXTA 10 MG, 50 MG AND 100 MG TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VENCLEXTA 10 mg tablets: each film-coated tablet contains 10 mg venetoclax.
VENCLEXTA 50 mg tablets: each film-coated tablet contains 50 mg venetoclax.
VENCLEXTA 100 mg tablets: each film-coated tablet contains 100 mg venetoclax.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

VENCLEXTA 10 mg tablets: round, biconvex shaped, pale yellow debossed with “V” on one side and “10” on the other side.
VENCLEXTA 50 mg tablets: oblong, biconvex shaped, beige debossed with “V” on one side and “50” on the other side.
VENCLEXTA 100 mg tablets: oblong, biconvex shaped, pale yellow debossed with “V” on one side and “100” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VENCLEXTA is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL).

VENCLEXTA is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.

4.2 Dose and method of administration

Method of Administration

VENCLEXTA should be taken orally once daily. Patients should be instructed to take VENCLEXTA tablets with a meal and water at approximately the same time each day. VENCLEXTA tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing (see section 5.2).

Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma

5-week Dose Titration Schedule

The starting dose of VENCLEXTA is 20 mg once daily for 7 days. The VENCLEXTA dose must be administered according to a weekly dose titration schedule to the daily dose of 400 mg over a period of 5 weeks as shown in Table 1.

The 5-week dose titration schedule is designed to gradually reduce tumour burden (debulking) and decrease the risk of tumour lysis syndrome (TLS).

Table 1. Dosing Schedule for Dose Titration Phase in Patients with CLL/SLL

Week	VENCLEXTA Daily Dose
1	20 mg
2	50 mg
3	100 mg
4	200 mg
5 and beyond	400 mg

The CLL/SLL Starting Pack provides the first 4 weeks of VENCLEXTA according to the dose titration schedule. The 400 mg dose is achieved using 100 mg tablets supplied in bottles (see section 6.5).

First line CLL/SLL

VENCLEXTA in Combination with Obinutuzumab

VENCLEXTA in combination with obinutuzumab should be given for a total of 12 cycles (28 days in each cycle) as shown in Table 2.

Table 2. Dosing Schedule for VENCLEXTA in Combination with Obinutuzumab

Cycle, Day	Obinutuzumab	VENCLEXTA
Cycle 1, Day 1	100 mg, followed by 900 mg which may be administered on Day 1 or 2	
Cycle 1, Day 8	1000 mg	
Cycle 1, Day 15	1000 mg	
Cycle 1, Day 22 – 28		20 mg daily[a]
Cycle 2, Day 1 – 7	Day 1 only: 1000 mg	50 mg daily[a]
Cycle 2, Day 8 – 14		100 mg daily[a]
Cycle 2, Day 15 – 21		200 mg daily[a]
Cycle 2, Day 22 – 28		400 mg daily[a]
Cycles 3 - 6, Day 1 - 28	Day 1 only: 1000 mg	400 mg daily
Cycles 7 - 12, Day 1 – 28		400 mg daily

[a]5 week dose titration (see Table 1)

Previously treated CLL/SLL

VENCLEXTA in Combination with Rituximab

Start rituximab administration after the patient has completed the dose titration schedule with VENCLEXTA (see Table 1) and has received a daily 400 mg dose of VENCLEXTA for 7 days.

Patients should continue VENCLEXTA 400 mg once daily for up to 24 months from Cycle 1 Day 1 of rituximab in the absence of disease progression or unacceptable toxicity.

VENCLEXTA as Monotherapy
The recommended dose of VENCLEXTA is 400 mg once daily after the patient has completed the dose titration schedule. Treatment should continue until disease progression or venetoclax is no longer tolerated by the patient.

Acute Myeloid Leukaemia

The dose of VENCLEXTA depends upon the combination agent. The VENCLEXTA dosing schedule (including the dose titration phase) is shown in Table 3.

Table 3. Dosing Schedule for Dose Titration Phase in Patients with AML

Day	VENCLEXTA Daily Dose	
1	100 mg	
2	200 mg	
3	400 mg	
4 and beyond	400 mg when dosing in combination with azacitidine	600 mg when dosing in combination with low-dose cytarabine

Initiate azacitidine or low-dose cytarabine on Cycle 1 Day 1.

Azacitidine should be administered at 75 mg/m^2 either intravenously or subcutaneously on Days 1-7 of each 28-day cycle beginning on Cycle 1 Day 1.

Cytarabine should be administered at a dose of 20 mg/m^2 subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1.

Interrupt VENCLEXTA dosing as needed for management of haematological toxicities and blood count recovery (see section 4.2 **Dose Modifications Based on Toxicities**). Refer to the azacitidine or cytarabine Data Sheet for additional information.

VENCLEXTA, in combination with azacitidine or low-dose cytarabine, should be continued until disease progression or unacceptable toxicity is observed.

Risk Assessment and Prophylaxis for Tumour Lysis Syndrome

Patients treated with VENCLEXTA may develop TLS. Refer to the appropriate section below for specific details on management. Assess patient-specific factors for level of risk of TLS and provide prophylactic hydration and anti-hyperuricaemics to patients prior to first dose of VENCLEXTA to reduce risk of TLS.

Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma

VENCLEXTA can cause rapid tumour reduction and thus poses a risk for TLS in the initial 5-week dose titration phase. Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of VENCLEXTA and at each dose increase.

The risk of TLS is a continuum based on multiple factors, including tumour burden and comorbidities, in particular reduced renal function (creatinine clearance [CrCl] <80mL/min), and tumour burden.

Splenomegaly may contribute to the overall TLS risk. The risk may decrease as tumour burden decreases with VENCLEXTA treatment (see section 4.4). Perform tumour burden assessments, including radiographic evaluation (e.g., CT scan). Assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) in all patients and correct pre-existing abnormalities prior to initiation of treatment with VENCLEXTA.

Prophylaxis for Tumour Lysis Syndrome

Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma

Table 4 below describes the recommended TLS prophylaxis and monitoring during VENCLEXTA treatment based on tumour burden determination from clinical trial data. In addition, consider all patient comorbidities for risk-appropriate prophylaxis and monitoring, either outpatient or in hospital.

Table 4. Recommended TLS Prophylaxis Based on Tumour Burden in Patients with CLL/SLL

Tumour Burden		Prophylaxis		Blood Chemistry Monitoring[c,d]
		Hydration[a]	Anti-hyperuricaemics[b]	Setting and Frequency of Assessments
Low	All LN <5 cm AND ALC <25 x 10^9/L	Oral (1.5-2L)	Allopurinol	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • For subsequent dose increases: Pre-dose
Medium	Any LN 5 cm to <10 cm OR ALC ≥25 x 10^9/L	Oral (1.5-2L) and consider additional intravenous	Allopurinol	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • For subsequent dose increases: Pre-dose • For first dose of 20 mg and 50 mg: Consider hospitalisation for patients with CrCl <80mL/min; see below for monitoring in hospital
High	Any LN ≥10 cm OR ALC ≥25 x 10^9/L AND any LN ≥5 cm	Oral (1.5-2L) and intravenous (150-200 mL/hr as tolerated)	Allopurinol; consider rasburicase if baseline uric acid is elevated	In hospital • For first dose of 20 mg and 50 mg: Pre-dose, 4, 8, 12 and 24 hours Outpatient • For subsequent dose increases: Pre-dose, 6 to 8 hours, 24 hours

ALC = absolute lymphocyte count; CrCl = creatinine clearance; LN = lymph node.
[a]Instruct patients to drink water daily starting 2 days before and throughout the dose titration phase, specifically prior to and on the days of dosing at initiation and each subsequent dose increase. Administer intravenous hydration for any patient who cannot tolerate oral hydration.
[b]Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of VENCLEXTA.
[c]Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.
[d]For patients at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent dose increase.

Acute Myeloid Leukaemia

The VENCLEXTA daily dose titration schedule is 3 days with azacitidine, or 4 days with low-dose cytarabine (see Table 3).

Follow these TLS prophylaxis measures:

- All patients should have white blood cell count $<25 \times 10^9$/L prior to initiation of VENCLEXTA and cytoreduction prior to treatment may be required.
- All patients should be adequately hydrated and receive anti-hyperuricaemic agents prior to initiation of the first dose of VENCLEXTA and during the dose titration schedule.
- Assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) and correct pre-existing abnormalities prior to initiation of treatment with VENCLEXTA.
    - Monitor blood chemistries for TLS at pre-dose, 6 to 8 hours after each new dose during the dose titration phase and 24 hours after reaching the final dose.
- For patients with risk factors for TLS (e.g., circulating blasts, high burden of leukaemia involvement in bone marrow, elevated pretreatment lactate dehydrogenase [LDH] levels, or reduced renal function), additional measures should be considered, including increased laboratory monitoring and reduced VENCLEXTA starting dose.

Dose Modifications Based on Toxicities

Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma

Dosing interruption and/or dose reduction for toxicities may be required. See Table 5 and Table 6 for recommended dose modifications for haematological and other toxicities related to VENCLEXTA. For patients who have had a dosing interruption greater than 1 week during the first 5 weeks of dose titration phase or greater than 2 weeks after completing the dose titration phase, reassess the risk of TLS to determine if re-initiation with a reduced dose is necessary (e.g., all or some levels of the dose titration schedule) (see section 4.2 **Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma 5-week Dose Titration Schedule, Risk Assessment and Prophylaxis for Tumour Lysis Syndrome** and **Prophylaxis for Tumour Lysis Syndrome**).

Table 5. Recommended VENCLEXTA Dose Modifications for Toxicities[a] in CLL/SLL

Event	Occurrence	Action
Tumour Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS	Any	Withhold the next day's dose. If resolved within 24-48 hours of last dose, resume at the same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose (see Table 6), (see section 4.2 **Risk Assessment and Prophylaxis for Tumour Lysis Syndrome** and **Prophylaxis for Tumour Lysis Syndrome**).
		For any events of clinical TLS, resume at a reduced dose following resolution (see Table 6), (see section 4.2 **Risk Assessment and Prophylaxis for Tumour Lysis Syndrome** and **Prophylaxis for Tumour Lysis Syndrome**).
Non-Haematological Toxicities		
Grade 3 or 4 non-haematological toxicities	1st occurrence	Interrupt VENCLEXTA. Once the toxicity has resolved to grade 1 or baseline level, VENCLEXTA therapy may be resumed at the same dose. No dose modification is required.
	2nd and subsequent occurrences	Interrupt VENCLEXTA. Follow dose reduction guidelines in Table 6 when resuming treatment with VENCLEXTA after resolution. A larger dose reduction may occur at the discretion of the physician.
Haematological Toxicities		
Grade 3 neutropenia with infection or fever; or grade 4 haematological toxicities (except lymphopenia) (see section 4.4; ***Neutropenia***)	1st occurrence	Interrupt VENCLEXTA. To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with VENCLEXTA if clinically indicated. Once the toxicity has resolved to grade 1 or baseline level, VENCLEXTA therapy may be resumed at the same dose.
	2nd and subsequent occurrences	Interrupt VENCLEXTA. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines in Table 6 when resuming treatment with VENCLEXTA after resolution. A larger dose reduction may occur at the discretion of the physician.
Consider discontinuing VENCLEXTA for patients who require dose reductions to less than 100 mg for more than 2 weeks. [a]Adverse reactions were graded using NCI CTCAE version 4.0. [b]Clinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or sudden death and/or seizures (see section 4.8).		

Table 6. Dose Reduction for Toxicity During VENCLEXTA Treatment of CLL/SLL

Dose at Interruption, mg	Restart Dose, mg[a]
400	300
300	200
200	100
100	50
50	20
20	10
[a]Continue the reduced dose for 1 week before increasing the dose.	

Acute Myeloid Leukaemia

Assess for remission at the end of Cycle 1. Recommend bone marrow assessment then and during treatment as needed and monitor blood counts frequently through resolution of cytopenias. Interrupt VENCLEXTA dosing as needed to manage adverse reactions or to allow for blood count recovery (see section 4.4 and section 4.8) or, if required, permanently discontinue VENCLEXTA. Table 7 shows the dose modification guidelines for Grade 4 neutropenia (ANC < 500/microliter) with or without fever or infection; or Grade 4 thrombocytopenia (platelet count < 25,000/microliter) (see section 4.4).

Table 7. Recommended Dose Modifications for Toxicities[a] During VENCLEXTA Treatment of AML

<table>
<tr><th colspan="3">Haematological Toxicities[a] Lasting >1 Week of Grade 4 Neutropenia With or Without Fever or Infection, or Grade 4 Thrombocytopenia</th></tr>
<tr><th>Before Remission[b] is Achieved</th><th colspan="2">After Remission[b] is Achieved</th></tr>
<tr><td rowspan="3">Transfuse blood products, administer prophylactic and treatment anti-infectives as clinically indicated.

In most instances, VENCLEXTA and azacitidine or low-dose cytarabine cycles should not be interrupted due to cytopenias prior to achieving remission.</td><td colspan="2">Delay subsequent treatment cycle of VENCLEXTA and azacitidine or low-dose cytarabine and monitor blood counts.

Administer granulocyte-colony stimulating factor (G-CSF) if clinically indicated for neutropenia.</td></tr>
<tr><th>For first occurrence</th><th>For subsequent occurrences</th></tr>
<tr><td>Once the toxicity has resolved to Grade 1 or 2, resume VENCLEXTA therapy at the same dose in combination with azacitidine or low-dose cytarabine.</td><td>Once the toxicity has resolved to Grade 1 or 2, resume VENCLEXTA therapy at the same dose in combination with azacitidine or low-dose cytarabine and reduce duration of VENCLEXTA administration by 7 days during each of the subsequent cycles, i.e., 21 days instead of 28 days.</td></tr>
<tr><td colspan="3">[a]Adverse reactions were graded using NCI CTCAE version 4.0.
[b]Bone marrow confirmation of <5% blasts with cytopenia.</td></tr>
</table>

Dose Modifications for Use with CYP3A Inhibitors

Concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors increases venetoclax exposure (i.e., C_{max} and AUC) and may increase the risk for TLS at initiation and during the dose titration phase.

In patients with CLL/SLL, concomitant use of VENCLEXTA with strong CYP3A inhibitors is contraindicated at initiation and during the dose titration phase (see section 4.3).

In all patients if a CYP3A inhibitor must be used, follow the recommendations for managing the drug-drug interactions summarised in Table 8. Monitor patients more closely for signs of toxicities (see section 4.2 **Dose Modifications Based on Toxicities**).

Resume the VENCLEXTA dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor (see section 4.2 **Dose Modifications Based on Toxicities** and section 4.5).

Table 8. Management of Potential VENCLEXTA Interactions with CYP3A Inhibitors

<table>
<tr><th>Inhibitors</th><th colspan="2">Initiation and Dose Titration Phase</th><th>Steady Daily Dose
(After Dose Titration Phase)[a]</th></tr>
<tr><td rowspan="2">Strong CYP3A inhibitor</td><td>CLL</td><td>Contraindicated</td><td rowspan="2">Reduce the VENCLEXTA dose to 100 mg or less.</td></tr>
<tr><td>AML</td><td>Day 1 – 10 mg
Day 2 – 20 mg
Day 3 – 50 mg
Day 4 – 100 mg or less</td></tr>
<tr><td>Moderate CYP3A inhibitor</td><td colspan="3">Reduce the VENCLEXTA dose by at least 50%.</td></tr>
<tr><td colspan="4">[a]In patients with CLL/SLL, avoid concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors. Consider alternative medications or reduce the VENCLEXTA dose as described in this table.</td></tr>
</table>

Missed Dose

If the patient misses a dose of VENCLEXTA within 8 hours of the time it is usually taken, the patient should be instructed to take the missed dose as soon as possible and resume the normal daily dosing schedule. If a patient misses a dose by more than 8 hours, the patient should not take the missed dose but resume the usual dosing schedule the next day.

If the patient vomits following dosing, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time.

Elderly Patients

No specific dose adjustment is required for elderly patients (aged ≥65 years; see section 5.1).

Patients with Renal Impairment

No specific clinical trials have been conducted in subjects with renal impairment. No dose adjustment is needed for patients with mild or moderate renal impairment (CrCl ≥30 mL/min), based on the results of the population pharmacokinetic analysis. Patients with reduced renal function (CrCl <80 mL/min) may require more intensive prophylaxis and monitoring to reduce the risk of TLS when initiating treatment with VENCLEXTA. While severe renal impairment (CrCl ≥15 mL/min and <30 mL/min) did not affect venetoclax pharmacokinetics in 6 patients with AML, clinical experience is limited and a recommended dose has not been determined for patients with severe renal impairment (CrCl <30 mL/min) or patients on dialysis (see section 5.2).

Patients with Hepatic Impairment

No dose adjustment is recommended in patients with mild or moderate hepatic impairment based on results of the population pharmacokinetic analysis. A 50% dose reduction throughout treatment is recommended for patients with severe hepatic impairment; monitor these patients more closely for signs of toxicity (see section 5.2– **Patients with hepatic impairment**).

Paediatric Population

The safety and efficacy of VENCLEXTA in children and adolescents less than 18 years of age have not been established.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

In patients with CLL or SLL, concomitant use of VENCLEXTA with strong CYP3A inhibitors at initiation and during the dose titration phase is contraindicated (see sections 4.2 and 4.5).

4.4 Special warnings and precautions for use

Tumour Lysis Syndrome

Tumour Lysis Syndrome, including life-threatening or fatal events and renal failure requiring dialysis, has occurred in patients treated with VENCLEXTA (see section 4.8).

Interrupt or discontinue VENCLEXTA, as recommended, if this adverse event occurs. When restarting VENCLEXTA, follow the dose modifications guidance (see section 4.2).

VENCLEXTA can cause rapid tumour reduction and thus poses a risk for TLS at initiation and during the dose titration phase. Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6-8 hours following the first dose of VENCLEXTA and at each dose increase.

The risk of TLS is a continuum based on multiple factors, including comorbidities (particularly reduced renal function), tumour burden (see Table 4), and splenomegaly in CLL (see section 4.2).

All patients should be assessed for risk and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricaemics. Blood chemistries should be monitored and abnormalities managed promptly. Employ more intensive measures (intravenous hydration, frequent monitoring, and hospitalisation) as overall risk increases (see section 4.2).

Concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors increases venetoclax exposure and may increase the risk of TLS at initiation and during dose titration phase (see sections 4.2 and 4.5). Inhibitors of P-gp may also increase venetoclax exposure (see section 4.5).

Neutropenia

In patients with CLL/SLL, grade 3 or 4 neutropenia has occurred in patients treated with VENCLEXTA in combination studies and monotherapy studies (see section 4.8). In patients with AML, grade 3 or 4 neutropenia is common before starting treatment. The neutrophil counts can worsen with VENCLEXTA in combination with azacitidine or low-dose cytarabine. Neutropenia can recur with subsequent cycles of therapy. Complete blood counts should be monitored throughout the treatment period. Dose interruptions or dose reductions are recommended for severe neutropenia. Supportive measures should be considered, including antimicrobials for any signs of infection, and use of growth factors (e.g. G-CSF) (see section 4.2).

Serious Infection

Serious infections, including events of sepsis and events with fatal outcome, have been reported in patients treated with VENCLEXTA (see section 4.8). Monitor patients for fever and any symptoms of infection and treat promptly. Interrupt dosing as appropriate.

Immunisation

The safety and efficacy of immunisation with live attenuated vaccines during or following VENCLEXTA therapy have not been studied. Do not administer live attenuated vaccines prior to, during, or after treatment with VENCLEXTA until B-cell recovery occurs.

4.5 Interaction with other medicines and other forms of interaction

Potential Effects of Other Medicines on VENCLEXTA

Venetoclax is predominantly metabolised by CYP3A4.

CYP3A Inhibitors

Co-administration of 400 mg once daily ketoconazole, a strong CYP3A, P-gp and BCRP inhibitor, for 7 days in 11 previously treated patients with NHL increased venetoclax C_{max} by 130% and AUC_{∞} by 540%.

Co-administration of 50 mg once daily ritonavir, a strong CYP3A, P-gp and OATP1B1/B3 inhibitor, for 14 days in 6 healthy subjects increased venetoclax C_{max} by 140% and AUC by 690%.

Compared with venetoclax 400 mg administered alone, co-administration of 300 mg posaconazole, a strong CYP3A and P-gp inhibitor, with venetoclax 50 mg and 100 mg for 7 days in 12 newly diagnosed patients with AML resulted in 61% and 86% higher venetoclax C_{max}, respectively. The venetoclax AUC_{24} was 90% and 144% higher, respectively.

For patients requiring concomitant use of VENCLEXTA with strong CYP3A inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, ritonavir) or moderate CYP3A inhibitors (e.g., ciprofloxacin, diltiazem, erythromycin, dronedarone, fluconazole, verapamil) administer VENCLEXTA dose according to Table 8. Monitor patients more closely for signs of VENCLEXTA toxicities (see section 4.2).

Resume the VENCLEXTA dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor (see section 4.2).

Avoid grapefruit products, Seville oranges, and starfruit during treatment with VENCLEXTA, as they contain inhibitors of CYP3A.

OATP1B1/1B3 and P-gp Inhibitors

Co-administration of a 600 mg single dose of rifampicin, an OATP1B1/1B3 and P-gp inhibitor, in 11 healthy subjects increased venetoclax C_{max} by 106% and AUC_{∞} by 78%.

Avoid concomitant use of venetoclax with P-gp inhibitors (e.g., amiodarone, captopril, carvedilol, ciclosporin, felodipine, quercetin, quinidine, ranolazine, ticagrelor) at initiation and during the dose titration phase; if a P-gp inhibitor must be used, patients should be monitored closely for signs of toxicities.

Azithromycin

Co-administration of 500 mg of azithromycin on the first day followed by 250 mg of azithromycin for 4 days in 12 healthy subjects decreased venetoclax C_{max} by 25% and AUC_{∞} by 35%. No dose adjustment is needed when venetoclax is co-administered with azithromycin.

CYP3A Inducers

Co-administration of 600 mg once daily rifampicin, a strong CYP3A inducer, for 13 days in 10 healthy subjects decreased venetoclax C_{max} by 42% and AUC_{∞} by 71%. Concomitant use of VENCLEXTA with strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampicin, St. John's wort (*Hypericum perforatum*)) or moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) should be avoided. Alternative treatments with less CYP3A induction should be considered (see section 5.2).

Gastric Acid Reducing Agents

Based on population pharmacokinetic analysis, gastric acid reducing agents (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) do not affect venetoclax bioavailability.

Potential Effects of VENCLEXTA on Other Medicines

Warfarin

In a drug-drug interaction study in three healthy volunteers, administration of a single 400 mg dose of venetoclax with 5 mg warfarin resulted in an 18% to 28% increase in C_{max} and AUC_{∞} of R-warfarin and S-warfarin. Because venetoclax was not dosed to steady state, it is recommended that the international normalised ratio (INR) be monitored closely in patients receiving warfarin.

P-gp Substrates

Administration of a single 100 mg dose of venetoclax with 0.5 mg digoxin, a P-gp substrate, in 10 healthy subjects resulted in a 35% increase in digoxin C_{max} and a 9% increase in digoxin AUC_{∞}. Therefore, co- administration of narrow therapeutic index P-gp substrates (e.g., digoxin, everolimus, and sirolimus) with VENCLEXTA should be avoided. If a narrow therapeutic index P-gp substrate must be used, it should be taken at least 6 hours before VENCLEXTA.

4.6 Fertility, pregnancy and lactation

Fertility

No human data on the effect of venetoclax on fertility are available. Based on findings in animals, male fertility may be compromised by treatment with VENCLEXTA.

Fertility and early embryonic development studies with venetoclax were conducted in male and female mice. These studies evaluated mating, fertilisation, and embryonic development through implantation. There were no effects of venetoclax on oestrus cycles, mating, fertility, corpora lutea, uterine implants or live embryos per litter at dosages up to 600 mg/kg/day (in male and female mice, approximately 2.8 to 3.2 times the human AUC exposure at a 400 mg dose). However, a risk to human male fertility exists based on testicular toxicity (germ cell loss) observed in dogs at all dose levels examined (exposures of 0.5 to 18 times the human AUC exposure at a 400 mg dose). Reversibility of this finding has not been demonstrated.

Pregnancy

Australian categorisation system for prescribing medicines in pregnancy: Category C.

There are no adequate and well-controlled studies of venetoclax in pregnant women. Based on embryo-foetal toxicity observed in mice, VENCLEXTA may have effects on the foetus when administered to pregnant women.

VENCLEXTA should not be used during pregnancy. Women of child-bearing potential must use highly effective contraceptive measures during treatment with VENCLEXTA and for at least 30 days after the last dose of treatment. If venetoclax is used during pregnancy or if the patient becomes pregnant while taking VENCLEXTA, the patient should be apprised of the potential hazard to a foetus. The time period following treatment with VENCLEXTA where it is safe to become pregnant is unknown.

Women of child-bearing potential should undergo pregnancy testing before initiation of VENCLEXTA.

In embryo-foetal development studies, venetoclax was administered to pregnant mice and rabbits. These studies evaluated potential effects after implantation and subsequent embryo-foetal development during the respective periods of major organogenesis in mice and rabbits. In mice, venetoclax was associated with increased post-implantation loss and decreased foetal body weight at 150 mg/kg/day (maternal exposures approximately 1.2 times the human AUC exposure at a 400 mg dose). In rabbits, venetoclax at 300 mg/kg/day produced maternal toxicity, but no foetal toxicity (maternal exposures approximately 0.14 times the human AUC exposure at a 400 mg dose). No teratogenicity was observed in either the mouse or the rabbit. Additionally, M27 administered at the maximum feasible dose of 250 mg/kg/day in a mouse embryo-foetal development study did not produce embryo-foetal toxicity or teratogenesis. The M27 dose of 250 mg/kg/day resulted in maternal exposures that were approximately 9 times the human M27 AUC exposure at a dose of 400 mg/day of venetoclax.

Breastfeeding

It is not known whether venetoclax or its metabolites are excreted in human breast milk. Available data in animals have shown excretion of venetoclax/metabolites in milk (see section 5.3). A risk to newborns/infants cannot be excluded. Because many drugs are excreted in human breast milk and because the potential for serious adverse reactions in breastfed infants from VENCLEXTA is unknown, nursing women should be advised to discontinue breastfeeding during treatment with VENCLEXTA.

4.7 Effects on ability to drive and use machines

No studies on the effects of VENCLEXTA on the ability to drive and use machines have been performed. The pharmacological activity and adverse events reported to date do not indicate that such an effect is likely.

4.8 Undesirable effects

Tabulated list of adverse reactions

Adverse reactions are listed below by MedDRA body system organ class, rate, and by frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing rate.

Clinical Trial Experience in CLL/SLL

Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

VENCLEXTA in Combination with Obinutuzumab

The safety of venetoclax in combination with obinutuzumab versus obinutuzumab and chlorambucil was evaluated in an open-label randomised (1:1) phase 3 study (CLL14/Study BO25323) in patients

with previously untreated CLL and coexisting medical conditions. Details of the study treatment are described in Section 5.1 **Clinical trials: VENCLEXTA in Combination with Obinutuzumab**.

At the time of data analysis, the median duration of exposure to venetoclax was 10.5 months (range: 1 to 13.5 months) and to obinutuzumab and chlorambucil for 6 and 12 cycles, respectively.

In the venetoclax + obinutuzumab arm, adverse events led to discontinuation in 16% of patients, dose reductions in 21% of patients and dose interruptions in 74% of patients. The most common adverse reaction that led to dose interruption of venetoclax was neutropenia.

Table 9 provides the adverse reactions reported in CLL14.

Table 9. Summary of Adverse Reactions Reported with Incidence of ≥10% and ≥5% Higher for all Grades or ≥2% Higher for Grade 3 or 4 in Patients Treated with VENCLEXTA + Obinutuzumab Compared with Obinutuzumab + Chlorambucil

Adverse Reaction by Body System	VENCLEXTA + Obinutuzumab (N=212)		Obinutuzumab + Chlorambucil (N=214)	
	All Grades % (Frequency)	Grade 3 or 4 %	All Grades %	Grade 3 or 4 %
Blood and lymphatic system disorders				
Neutropenia[a]	60 (Very common)	56	62	52
Gastrointestinal disorders				
Diarrhoea	28 (Very common)	4	15	<1
[a]Includes neutropenia and neutrophil count decreased.				

Other adverse reactions reported in the venetoclax + obinutuzumab arm are presented below:

Blood and lymphatic system disorders: anaemia (17%), febrile neutropenia (6%), lymphopenia (1%)

Gastrointestinal disorders: nausea (19%), constipation (13%), vomiting (10%)

General disorders and administration site conditions: fatigue (15%)

Infection and infestation disorder: pneumonia (8%), upper respiratory tract infection (8%), urinary tract infection (5%), sepsis[a] (4%)

Investigations: blood creatinine increased (3%)

Metabolism and nutrition disorder: hyperuricaemia (4%), hyperkalaemia (2%), hyperphosphataemia (2%), hypocalcaemia (1%), tumour lysis syndrome (1%)

[a]Includes the following terms: sepsis, septic shock, and urosepsis.

VENCLEXTA in Combination with Rituximab

Summary of the safety profile

The safety of venetoclax in combination with rituximab versus bendamustine in combination with rituximab, was evaluated in an open-label randomised phase 3 study (MURANO/Study GO28667), in patients with CLL who have received at least one prior therapy. Details of the study treatment are

described in Section 5.1 **Clinical Efficacy and Safety: VENCLEXTA in Combination with Rituximab**. At the time of data analysis, the median duration of exposure was 22 months in the venetoclax + rituximab arm compared to 6 months in the bendamustine plus rituximab arm.

Discontinuations due to adverse events occurred in 16% of patients treated with venetoclax + rituximab. Dose reductions due to adverse events occurred in 15% of patients treated with venetoclax + rituximab. Dose interruptions due to adverse events occurred in 71% of patients treated with venetoclax + rituximab. The most common adverse reaction that led to dose interruption of venetoclax was neutropenia.

The frequencies of adverse drug reactions (ADRs) reported in patients treated with venetoclax + rituximab are summarised in Table 10.

Table 10. Summary of Adverse Reactions Reported in ≥10% Incidence and ≥5% higher [All Grades] OR ≥2% higher [Grade 3 or 4] in Patients treated with VENCLEXTA plus rituximab compared with Bendamustine plus Rituximab

Adverse Reaction by Body System	VENCLEXTA + Rituximab (N=194)		Bendamustine + Rituximab (N=188)	
	All Grades % (Frequency)	Grade 3 or 4 %	All Grades %	Grade 3 or 4 %
Blood and lymphatic system disorders				
Neutropenia	61 (Very common)	58	44	39
Gastrointestinal disorders				
Diarrhoea	40 (Very common)	3	17	1
Infections and infestations				
Upper respiratory tract infection	22 (Very common)	2	15	1
Metabolism and nutrition disorders				
Tumour lysis syndrome	3 (Common)	3	1	1

Based on the existing safety profile of VENCLEXTA, other adverse reactions reported in the venetoclax + rituximab arm of MURANO include:

Blood and lymphatic system disorders: anaemia (16%), febrile neutropenia (4%), lymphopenia (0%; considered an adverse reaction based on the mechanism of action)

Gastrointestinal disorders: nausea (21%), constipation (14%), vomiting (8%)

General disorders and administration site conditions: fatigue (18%)

Infections and infestations: pneumonia (9%), urinary tract infections (6%), sepsis (1%)

Investigations: blood creatinine increase (3%)

Metabolism and nutrition disorders: hyperkalaemia (6%), hyperphosphataemia (5%), hyperuricaemia (4%), hypocalcaemia (2%).

During treatment with single agent VENCLEXTA after completion of venetoclax + rituximab combination treatment, the most common all grade adverse reactions (≥10% patients) reported were diarrhoea (19%), neutropenia (14%), and upper respiratory tract infection (12%); the most common grade 3 or 4 adverse reaction (≥2% patients) was neutropenia (11%).

VENCLEXTA as Monotherapy

The safety of VENCLEXTA is based on pooled data of 352 patients treated with VENCLEXTA in two phase 2 trials (M13-982 and M14-032) and one phase 1 trial (M12-175). The trials enrolled patients with previously treated CLL or SLL, including 212 patients with 17p deletion and 148 patients who had failed an inhibitor of the B-cell receptor pathway. Patients were treated with VENCLEXTA 400 mg monotherapy once daily following the dose titration schedule.

Summary of the safety profile

The most frequently reported serious adverse reactions (≥2%) unrelated to disease progression were pneumonia and febrile neutropenia.
Discontinuations due to adverse events occurred in 9% of patients.

Dosage reductions due to adverse events occurred in 13% of patients. Dose interruptions due to adverse events occurred in 36% of patients. Of the most frequent adverse events (≥4%) leading to dose reductions or interruptions, the one identified as adverse reaction was neutropenia (5% and 4%, respectively).

The frequencies of adverse drug reactions (ADRs) identified in the three trials of patients with previously treated CLL using VENCLEXTA monotherapy are summarised in Table 11.

Table 11. Adverse drug reactions identified in patients with CLL treated with VENCLEXTA monotherapy

Adverse Reaction by Body System	All Grades Frequency N=352	All Grades % N=352	Grade 3 or 4 % N=352
Blood and lymphatic system disorders			
Neutropenia[a]	Very common	50	45
Anaemia[b]	Very common	33	18
Lymphopenia[c]	Very common	11	7
Febrile neutropenia	Common	6	6
Gastrointestinal disorders			
Diarrhoea	Very common	43	3
Nausea	Very common	42	1
Vomiting	Very common	16	1
Constipation	Very common	16	<1
General disorders and administration site conditions			
Fatigue	Very common	30	3
Infections and infestations			
Upper respiratory tract infection	Very common	26	1
Pneumonia	Very common	12	7
Urinary tract infection	Common	9	1
Sepsis[d]	Common	5	3
Investigations			
Blood creatinine increased	Common	8	<1
Metabolism and nutrition disorders[e]			
	N=168	N=168 All grades	N=168 Grade ≥3
Tumour lysis syndrome[f]	Common	2	2
Hyperkalaemia[g]	Very common	17	1
Hyperphosphataemia[h]	Very common	14	2
Hyperuricaemia[i]	Common	10	<1
Hypocalcaemia[j]	Very common	16	2

[a]Includes neutropenia and neutrophil count decreased.
[b]Includes anaemia and haemoglobin decreased.
[c]Includes lymphopenia and lymphocyte count decreased.
[d]Includes escherichia sepsis, sepsis, septic shock, urosepsis, corynebacterium bacteraemia, corynebacterium sepsis, klebsiella bacteraemia, klebsiella sepsis, pulmonary sepsis, staphylococcal bacteraemia, and staphylococcal sepsis.
[e]Adverse reactions for this body system are reported for patients who followed the 5-week dose titration dosing schedule and TLS prophylaxis and monitoring measures described in Section 4.2.
[f]Reported as TLS events.
[g]Includes hyperkalaemia and blood potassium increased.
[h]Includes hyperphosphataemia and blood phosphorus increased.
[i]Includes hyperuricaemia and blood uric acid increased.
[j]Includes hypocalcaemia and blood calcium decreased.

Clinical Trial Experience in AML

VENCLEXTA in Combination with Azacitidine

VIALE-A

The safety of VENCLEXTA in combination with azacitidine (N=283) versus placebo with azacitidine (N=144) was evaluated in a double-blind randomised phase 3 study, in patients with newly diagnosed AML. Details of the study treatment are described in Section 5.1 (see section 5.1 **Clinical efficacy and safety**).

The median duration of treatment was 7.6 months (range: <0.1 to 30.7 months) in the VENCLEXTA in combination with azacitidine arm and 4.3 months (range: 0.1 to 24.0 months) in the placebo with azacitidine arm. The median number of cycles of azacitidine was 7.0 (range: 1.0 to 30.0) in the VENCLEXTA in combination with azacitidine arm and 4.5 (range: 1.0 to 26.0) in the placebo with azacitidine arm.

In the VENCLEXTA in combination with azacitidine arm, serious adverse reactions were reported in 83% of patients, with most frequent (≥5%) being febrile neutropenia (30%), pneumonia (23%), and sepsis (16%). In the placebo with azacitidine arm, serious adverse reactions were reported in 73% of patients.

In the VENCLEXTA in combination with azacitidine arm, adverse reactions led to venetoclax treatment discontinuations in 24% of patients, venetoclax dose reductions in 2%, and venetoclax dose interruptions in 72%. Among patients who achieved bone marrow clearance of leukaemia, 53% underwent dose interruptions for ANC <500/microliter. In the placebo with azacitidine arm, adverse reactions led to placebo treatment discontinuations in 20% of patients, placebo dose reductions in 4%, and placebo dose interruptions in 57%.

In the VENCLEXTA in combination with azacitidine arm no event led to venetoclax discontinuation in ≥ 5% of patients.

The most frequent adverse reactions (≥5%) leading to venetoclax dose interruptions in the VENCLEXTA in combination with azacitidine arm were febrile neutropenia (20%), neutropenia (20%), pneumonia (14%), thrombocytopenia (10%), and sepsis (8%). In the placebo with azacitidine arm, the most frequent adverse reaction (≥5%) leading to placebo dose interruption were pneumonia (14%), neutropenia (10%) and sepsis (6%).

The 30-day and 60-day mortality rates observed with VENCLEXTA in combination with azacitidine were 7% (21/283) and 15% (43/283), respectively.

Table 12 provides the adverse reactions reported in VIALE-A.

Table 12. Common (≥10%) Adverse Reactions Reported with ≥5% Higher (All Grades) or ≥2% Higher (Grade ≥3) Incidence in Patients Treated with VENCLEXTA + Azacitidine Compared with Placebo + Azacitidine

Adverse Reaction by Body System	All Grades Frequency	VENCLEXTA + Azacitidine (N = 283)		Placebo + Azacitidine (N = 144)	
		All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Blood and lymphatic system disorders					
Thrombocytopenia[a]	Very common	51	48	41	38
Neutropenia[b]	Very common	45	45	30	28
Febrile neutropenia	Very common	42	42	19	19
Anaemia[c]	Very common	28	26	21	20
Gastrointestinal disorders					
Nausea	Very common	44	2	35	<1
Diarrhoea	Very common	41	5	33	3
Vomiting	Very common	30	2	23	<1
Stomatitis	Very common	12	<1	6	0
General disorders and administration site conditions					
Fatigue	Very common	21	3	17	1
Asthenia	Very common	16	4	8	<1
Infections and infestations					
Sepsis[d]	Very common	18	18	14	14
Metabolism and nutrition disorders					
Decreased appetite	Very common	25	4	17	<1
Musculoskeletal and connective tissue disorders					
Arthralgia	Very common	12	<1	5	0
Nervous system disorder					
Dizziness/syncope[e]	Very common	19	4	8	1
Respiratory, thoracic and mediastinal disorders					
Dyspnoea	Very common	13	3	8	2
Vascular disorder					
Haemorrhage[f]	Very common	38	10	37	6
Hypotension	Very common	10	5	6	3

[a]Includes thrombocytopenia and platelet count decreased.
[b]Includes neutropenia and neutrophil count decreased.
[c]Includes anaemia and haemoglobin decreased.
[d]Includes sepsis, escherichia sepsis, septic shock, bacteraemia, staphylococcal sepsis, klebsiella sepsis, pseudomonal sepsis, urosepsis, bacterial sepsis, candida sepsis, clostridial sepsis, enterococcal sepsis, fungal sepsis, neutropenic sepsis, and streptococcal sepsis.
[e]Includes vertigo, dizziness, syncope, and presyncope.
[f]Includes multiple terms; epistaxis, petechiae and haematoma occurred in ≥5% of patients.

Other adverse reactions (all grades) reported in the venetoclax + azacitidine arm are presented below:

Gastrointestinal disorders: abdominal pain (11%)

Hepatobiliary disorders: cholecystitis/cholelithiasis[a] (4%)

Infections and infestations: pneumonia[b] (34%), urinary tract infection (9%)

Investigations: blood bilirubin increased (7%), weight decreased (13%)

Metabolism and nutrition disorders: hypokalaemia (29%), tumour lysis syndrome (1%)

Nervous System Disorders: headache (11%).

[a]Includes following terms: cholecystitis acute, cholelithiasis, cholecystitis, and cholecystitis chronic.

[b]Includes following terms: pneumonia, lung infection, bronchopulmonary aspergillosis, pneumonia fungal, pneumonia klebsiella, atypical pneumonia, pneumonia viral, infectious pleural effusion, pneumonia haemophilus, pneumonia pneumococcal, pneumonia respiratory syncytial viral, pulmonary mycosis, pulmonary nocardiosis, and tuberculosis.

M14-358

The safety of VENCLEXTA in combination with azacitidine (N=84) was evaluated in a non-randomised study, in patients with newly diagnosed AML.

The most common adverse reactions (≥30%) of any grade were nausea (64%), diarrhoea (61%), thrombocytopenia/platelet count decreased (54%), neutropenia/neutrophil count decreased (46%), hypokalaemia (35%), febrile neutropenia (39%), vomiting (38%), fatigue (36%), and pneumonia[a] (38%).

Serious adverse events were reported in 77% of patients. The most frequent serious adverse reactions (≥5%) were febrile neutropenia and pneumonia.

Discontinuations of VENCLEXTA due to adverse events occurred in 25% of patients. The most frequent adverse reactions leading to drug discontinuation (≥2%) were febrile neutropenia and pneumonia.

Dosage interruptions of VENCLEXTA due to adverse events occurred in 68% of patients. The most frequent adverse reactions leading to dose interruption (≥5%) were febrile neutropenia, neutropenia/neutrophil count decreased, and pneumonia.

Dosage reductions of VENCLEXTA due to adverse reactions occurred in 1% of patients. Dose reduction occurred in 1 patient, due to neutrophil count decreased.

The 30-day and 60-day mortality rates observed with VENCLEXTA in combination with azacitidine were 2.4% (2/84) and 8.3% (7/84), respectively.

[a]Includes the following terms: Pneumonia, lung consolidation, and pneumonia fungal.

VENCLEXTA in Combination with Low-Dose Cytarabine

VIALE-C

The safety of VENCLEXTA (600 mg daily dose) in combination with low-dose cytarabine (N=142) versus placebo with low-dose cytarabine (N=68) was evaluated in a double-blind randomised phase 3 study (based on 6-month follow-up data), in patients with newly diagnosed AML (see section 5.1 **Clinical efficacy and safety**).

The median duration of treatment was 4.1 months (range: <0.1 to 23.5 months) in the VENCLEXTA in combination with low-dose cytarabine arm and 1.7 months (range: 0.1 to 20.2 months) in the placebo with low-dose cytarabine arm. The median number of cycles of low-dose cytarabine was 4 (range: 1.0 to 22.0) in the VENCLEXTA in combination with low-dose cytarabine arm and 2 (range: 1.0 to 22.0) (28 days per cycle) in the placebo with low-dose cytarabine arm.

Serious adverse reactions were reported in 67% of patients in the VENCLEXTA in combination with low-dose cytarabine arm, with the most frequent (≥10%) being pneumonia (20%), febrile neutropenia (17%), and sepsis (13%). In the placebo with low-dose cytarabine arm, serious adverse reactions were reported in 62% of patients. The most frequent were febrile neutropenia (18%), sepsis (18%), and pneumonia (16%).

In the VENCLEXTA in combination with low-dose cytarabine arm, adverse reactions led to treatment discontinuations in 26% of patients, venetoclax dose reductions in 10%, and venetoclax dose interruptions in 63%. Among patients who achieved bone marrow clearance of leukaemia, 37% underwent dose interruptions for ANC <500/microliter. In the placebo with low-dose cytarabine arm, adverse reactions led to placebo treatment discontinuations in 24% of patients, placebo dose reductions in 7%, and placebo dose interruptions in 51%.

The most frequent adverse reaction leading to venetoclax discontinuation in the VENCLEXTA in combination with low-dose cytarabine arm was pneumonia (7%); sepsis (4%) was the most frequent adverse reaction leading to discontinuation in the placebo with low-dose cytarabine arm.

The most frequent adverse reactions (≥2%) leading to dose reductions in the VENCLEXTA in combination with low-dose cytarabine arm was thrombocytopenia (2%). The most frequent adverse reactions (≥5%) leading to dose interruption in the VENCLEXTA in combination with low-dose cytarabine arm were neutropenia (23%), thrombocytopenia (15%), pneumonia (8%), febrile neutropenia (8%), and anaemia (6%), and in the placebo with low-dose cytarabine arm were pneumonia (12%), thrombocytopenia (9%), febrile neutropenia (7%), neutropenia (6%), and sepsis (6%).

The 30-day and 60-day mortality rates observed with VENCLEXTA in combination with low-dose cytarabine were 13% (18/142) and 20% (29/142), respectively.

Table 13 presents adverse reactions identified in the VIALE-C trial data based on 6-month follow-up.

Table 13. Common (≥10%) Adverse Reactions Reported with ≥5% Higher (All Grades) or ≥2% Higher (Grade ≥3) Incidence in Patients Treated with VENCLEXTA + Low-Dose Cytarabine Compared with Placebo + Low-Dose Cytarabine

Adverse Reaction by Body System	All Grades Frequency	VENCLEXTA + Low-Dose Cytarabine (N = 142)		Placebo + Low-Dose Cytarabine (N = 68)	
		All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Blood and lymphatic system disorders					
Thrombocytopenia[a]	Very common	50	50	46	44
Neutropenia[b]	Very common	53	53	22	21
Febrile neutropenia	Very common	32	32	29	29
Anaemia	Very common	29	27	22	22
Gastrointestinal disorders					
Nausea	Very common	43	1	31	0
Diarrhoea	Very common	33	3	18	0
Vomiting	Very common	29	<1	15	0
Abdominal pain	Very common	12	0	4	1
Infections and infestations					
Pneumonia[c]	Very common	30	25	22	22
Investigations					
Blood bilirubin increased	Very common	11	2	1	0
Metabolism and nutrition disorders					
Hypokalaemia	Very common	31	12	25	16
Nervous System Disorders					
Headache	Very common	14	0	4	0
Dizziness/syncope[d]	Very common	14	2	6	0
Vascular Disorders					
Haemorrhage[e]	Very common	42	11	31	7

[a]Includes thrombocytopenia and platelet count decreased.
[b]Includes neutropenia and neutrophil count decreased.
[c]Includes pneumonia, lung infection, pneumonia fungal, pulmonary mycosis, bronchopulmonary aspergillosis, pneumocystis jirovecii pneumonia, pneumonia cytomegaloviral, pneumonia pseudomonal.
[d]Includes vertigo, dizziness, syncope, and presyncope.
[e]Includes multiple terms; no events occurred in ≥5% of patients.

Other adverse drug reactions reported in the venetoclax + low-dose cytarabine arm are presented below:

Gastrointestinal disorder: stomatitis (10%)

General disorders and administration site conditions: fatigue (16%), asthenia (12%)

Hepatobiliary disorders: cholecystitis/cholelithiasis[a] (2%)

Infections and infestations: sepsis[b] (15%), urinary tract infection (7%)

Investigations: weight decreased (10%)

Metabolism and nutrition disorders: decreased appetite (22%), tumour lysis syndrome (6%)

Musculoskeletal and connective tissue disorders: arthralgia (8%)

Respiratory, thoracic and mediastinal disorders: dyspnoea (8%)

Vascular disorders: hypotension (10%).

[a]Includes following terms: cholecystitis acute, cholecystitis, and cholecystitis chronic.

[b]Includes following terms: sepsis, septic shock, bacteraemia, neutropenic sepsis, bacterial sepsis, and staphylococcal sepsis.

M14-387
The safety of VENCLEXTA in combination with low-dose cytarabine (N=82) was evaluated in a non-randomised study, in patients with newly diagnosed AML.

The most common adverse reactions (≥30%) of any grade were nausea (70%), thrombocytopenia/platelet count decreased (61%), diarrhoea (50%), hypokalaemia (49%) neutropenia/neutrophil count decreased (46%), febrile neutropenia (44%), fatigue (43%), decreased appetite (37%), anaemia/haemoglobin decreased (32%), and vomiting (30%).

Serious adverse events were reported in 91% of patients. The most frequent serious adverse reactions (≥5%) were febrile neutropenia, pneumonia, and sepsis.

Discontinuations of VENCLEXTA due to adverse events occurred in 33% of patients. The most frequent adverse reactions leading to venetoclax discontinuation (≥2%) were thrombocytopenia, sepsis, and haemorrhage intracranial.

Dosage interruptions of VENCLEXTA due to adverse events occurred in 59% of patients. The most frequent adverse reactions leading to venetoclax interruption (≥5%) were thrombocytopenia and neutropenia.

Dosage reductions of VENCLEXTA due to adverse events occurred in 7% of patients. The most frequent adverse reaction leading to dose reduction (≥2%) was thrombocytopenia.

Important Adverse Reactions

Tumour Lysis Syndrome
Tumour lysis syndrome is an important identified risk when initiating VENCLEXTA.

Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma

VENCLEXTA as Monotherapy (Studies M13-982 and M14-032)
In the initial Phase 1 dose-finding trials, which had a relatively short (2-3 week) dose titration phase and higher starting dose, the incidence of TLS was 13% (10/77; 5 laboratory TLS, 5 clinical TLS), including 2 fatal events and 3 events of acute renal failure, 1 requiring dialysis.

The risk of TLS was reduced after revision of the dosing regimen and modification to prophylaxis and monitoring measures (see section 4.2). In venetoclax clinical trials, patients with any measurable lymph node ≥10 cm or those with both an ALC ≥25 x 10^9/L and any measurable lymph node ≥5 cm were hospitalised to enable more intensive hydration and monitoring for the first day of dosing at 20 mg and 50 mg during the dose titration phase.

In 168 patients with CLL starting with a daily dose of 20 mg and increasing over 5 weeks to a daily dose of 400 mg in studies M13-982 and M14-032, the rate of TLS was 2%. All events were laboratory TLS (laboratory abnormalities that met ≥2 of the following criteria within 24 hours of each other: potassium >6 mmol/L, uric acid >476 µmol/L, calcium <1.75 mmol/L, or phosphorus >1.5 mmol/L); or were reported as TLS events and occurred in patients who had a lymph node(s) ≥5 cm and/or ALC ≥25 x 10^9/L. All events resolved within 5 days. No TLS with clinical consequences such as acute renal failure, cardiac arrhythmias or sudden death and/or seizures was observed in these patients. All patients had CrCl ≥50 mL/min.

VENCLEXTA in Combination with Rituximab

In the open-label, randomised phase 3 study (MURANO), the incidence of TLS was 3% (6/194) in patients treated with venetoclax + rituximab. After 77/389 patients were enrolled in the study, the protocol was amended to include the TLS prophylaxis and monitoring measures described in Dosage and Administration section (see section 4.2). All events of TLS occurred during the VENCLEXTA dose titration phase and resolved within two days. All six patients completed the dose titration and reached the recommended daily dose of 400 mg of VENCLEXTA. No clinical TLS was observed in patients who followed the current 5-week dose titration dosing schedule and TLS prophylaxis and monitoring measures described (see section 4.2). The rates of grade ≥3 laboratory abnormalities relevant to TLS were hyperkalaemia 1%, hyperphosphataemia 1%, and hyperuricaemia 1%.

VENCLEXTA in Combination with Obinutuzumab

In the open-label, randomised phase 3 study (CLL14), the incidence of TLS was 1% (3/212) in patients treated with venetoclax + obinutuzumab (see section 4.4 **Tumour Lysis Syndrome**). All three events of TLS resolved and did not lead to withdrawal from the study. Obinutuzumab administration was delayed in two cases in response to the TLS events.

Acute Myeloid Leukaemia

VENCLEXTA in Combination with Azacitidine (VIALE-A) and VENCLEXTA in Combination with Low-Dose Cytarabine (VIALE-C)

In the randomised, phase 3 study (VIALE-A) with venetoclax in combination with azacitidine the incidence of TLS was 1.1% (3/283, 1 clinical TLS) and in the phase 3 study (VIALE-C), the incidence of TLS was 5.6% (8/142, 4 clinical TLS, 2 of which were fatal). The studies required reduction of white blood cell count to <25 x 10^9/L prior to venetoclax initiation and dose titration in addition to standard prophylaxis and monitoring measures (see section 4.2 **Dose Modifications Based on Toxicities**). All cases of TLS occurred during the dose titration phase.

Neutropenia

Neutropenia is an identified risk associated with VENCLEXTA treatment.

Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma

VENCLEXTA in Combination with Rituximab

In MURANO, neutropenia (all grades) was reported in 61% of patients on the venetoclax + rituximab arm. Forty-three percent of patients treated with venetoclax + rituximab experienced dose interruption and 3% of patients discontinued venetoclax due to neutropenia. Grade 3 neutropenia was reported in 32% of patients and grade 4 neutropenia in 26% of patients. The median duration of grade 3 or 4 neutropenia was 8 days (range: 1-712 days). Clinical complications of neutropenia, including febrile neutropenia, grade ≥3 and serious infections occurred at a lower rate in patients treated with venetoclax + rituximab arm compared with the rates reported in patients treated with bendamustine + rituximab: febrile neutropenia 4% versus 10%, grade ≥3 infections 18% versus 23%, and serious infections 21% versus 24%.

VENCLEXTA in Combination with Obinutuzumab

In CLL14, neutropenia (all grades) was reported in 58% of patients in the venetoclax + obinutuzumab arm. Forty-one percent experienced dose interruption, 13% had dose reduction and 2% discontinued venetoclax due to neutropenia. Grade 3 neutropenia was reported in 25% of patients and grade 4 neutropenia in 28% of patients. The median duration of grade 3 or 4 neutropenia was 22 days (range: 2 to 363 days). The following complications of neutropenia were reported in the venetoclax + obinutuzumab arm versus the obinutuzumab + chlorambucil arm, respectively: febrile neutropenia 6% versus 4%, grade ≥3 infections 19% versus 16%, and serious infections 19% versus 14%.

Acute Myeloid Leukaemia

VENCLEXTA in Combination with Azacitidine

In the VIALE-A study, grade ≥3 neutropenia was reported in 45% of patients. The following were reported in the venetoclax + azacitidine arm versus the placebo + azacitidine arm, respectively: febrile neutropenia 42% versus 19%, grade ≥3 infections 64% versus 51%, and serious infections 57% versus 44%.

VENCLEXTA in Combination with Low-Dose Cytarabine

In the VIALE-C study, grade ≥3 neutropenia was reported in 53% of patients. The following were reported in the venetoclax + low-dose cytarabine arm versus the placebo + low-dose cytarabine arm, respectively: febrile neutropenia 32% versus 29%, grade ≥3 infections 43% versus 50%, and serious infections 37% versus 37%.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Daily doses of up to 1200 mg of VENCLEXTA have been evaluated in clinical trials. There has been no experience with overdose in clinical trials. If an overdose is suspected, treatment should consist of general supportive measures.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: L01XX52.

Mechanism of action

Venetoclax is an orally bioavailable small-molecule inhibitor of B-cell lymphoma (BCL)-2, an anti-apoptotic protein. Overexpression of BCL-2 has been demonstrated in chronic lymphocytic leukaemia (CLL) cells and has been implicated in resistance to certain therapeutic agents. Venetoclax helps restore the process of apoptosis by binding directly to the BCL-2 protein, displacing pro-apoptotic proteins like BIM, triggering mitochondrial outer membrane permeabilisation, the release of cytochrome *c* from

mitochondria and the activation of caspases. In nonclinical studies, venetoclax demonstrated cytotoxic activity in tumour cells that overexpress BCL-2.

Cardiac Electrophysiology

The effect of multiple doses of VENCLEXTA up to 1200 mg once daily on the QTc interval was evaluated in an open-label, single-arm study in 176 patients with previously treated CLL or Non-Hodgkin Lymphoma (NHL). VENCLEXTA had no effect on QTc interval and there was no relationship between venetoclax exposure and change in QTc interval.

Clinical efficacy and safety

Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma

VENCLEXTA in Combination with Obinutuzumab

CLL14 (Study BO25323)

CLL14 was a randomised (1:1), multicentre, open label phase 3 study that evaluated the efficacy and safety of VENCLEXTA in combination with obinutuzumab versus obinutuzumab in combination with chlorambucil for previously untreated CLL in patients with coexisting medical conditions (total Cumulative Illness Rating Scale [CIRS] score > 6 or creatinine clearance < 70 mL/min). Patients in the study were assessed for risk of TLS and received prophylaxis accordingly prior to obinutuzumab administration. All patients received obinutuzumab at 1000 mg on Cycle 1 Day 1 (the first dose could be split as 100 mg and 900 mg on Days 1 and 2), and 1000 mg doses on Days 8 and 15 of Cycle 1, and on Day 1 of each subsequent cycle, for a total of 6 cycles. On Day 22 of Cycle 1, patients in the venetoclax + obinutuzumab arm began the 5-week VENCLEXTA dose titration schedule (see section 4.2). After completing the dose titration schedule on Cycle 2 Day 28, patients received VENCLEXTA 400 mg once daily from Cycle 3 Day 1 until the last day of Cycle 12. Patients randomised to the obinutuzumab + chlorambucil arm received 0.5 mg/kg oral chlorambucil on Day 1 and Day 15 of Cycles 1 to 12, in the absence of disease progression or unacceptable toxicity. Each cycle was 28 days. Following completion of 12 cycles of VENCLEXTA, patients continued to be followed for disease progression and overall survival.

Baseline demographic and disease characteristics were similar between the study arms (Table 14).

Table 14. Demographics and Baseline Characteristics in CLL14

Characteristic	VENCLEXTA + Obinutuzumab (N = 216)	Obinutuzumab + Chlorambucil (N = 216)
Age, years; median (range)	72 (43-89)	71 (41-89)
White; %	89	90
Male; %	68	66
ECOG performance status; %		
0	41	48
1	46	41
2	13	12
CIRS score, median (range)	9 (0-23)	8 (1-28)
Creatinine clearance < 70 mL/min; %	60	56
Binet Stage at screening; %		
A	21	20
B	36	37
C	43	43

At baseline, the median lymphocyte count was 55 x 10^9 cells/L in both study arms. On Cycle 1 Day 15, the median count decreased to 1.03 x 10^9 cells/L (range 0.2-43.4 x 10^9 cells/L) in the obinutuzumab + chlorambucil arm compared with 1.27 x 10^9 cells/L (range 0.2-83.7 x 10^9 cells/L) in the venetoclax + obinutuzumab arm.

The median follow-up at the time of analysis was 28 months (range: 0 to 36 months).

The primary endpoint was progression-free survival (PFS) as assessed by investigators using the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008).

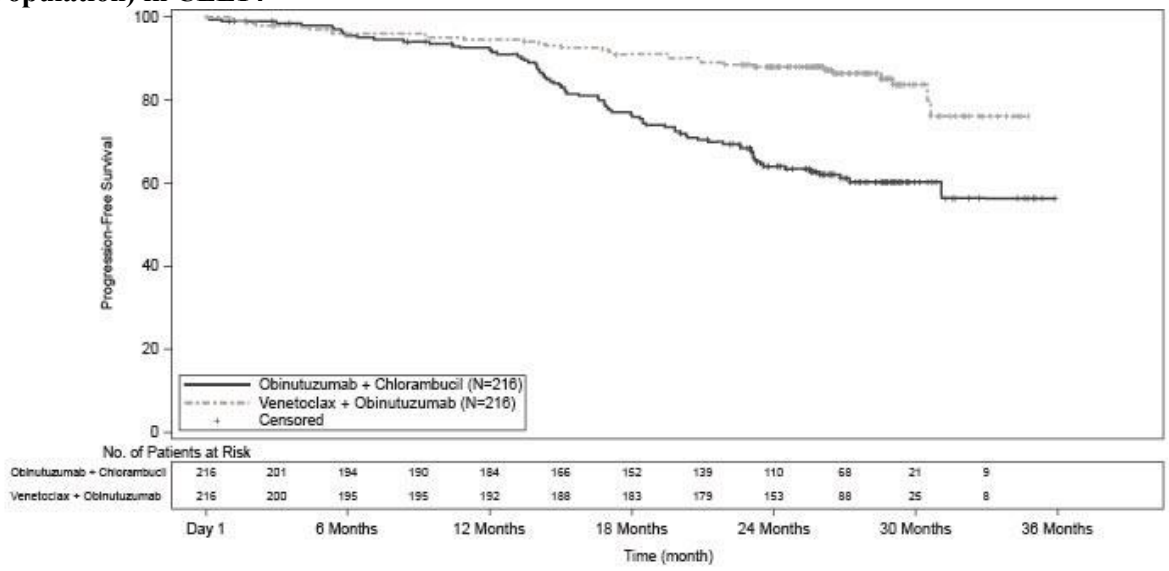
Efficacy results for CLL14 are shown in Table 15. The Kaplan-Meier curve for PFS is shown in Figure 1.

Table 15. Efficacy Results for CLL14

	VENCLEXTA + Obinutuzumab (N = 216)	**Obinutuzumab + Chlorambucil (N = 216)**
Progression-free survival, investigator-assessed		
Number of events (%)	30 (13.9)	77 (36)
Median, months,	Not Reached	Not Reached
HR (95% CI)	0.35 (0.23, 0.53)	
p-value	<0.0001	
12-month estimate, % (95% CI)	94.6 (91.5, 97.7)	92.1 (88.4, 95.8)
24-month estimate, % (95% CI)	88.2 (83.7, 95.1)	64.1 (57.4, 70.8)
Progression-free survival, IRC-assessed		
Number of events (%)	29 (13)	79 (37)
Median, months,	Not Reached	Not Reached
HR (95% CI)	0.33 (0.22, 0.51)	
p-value	<0.0001	
12-month estimate, % (95% CI)	94.6 (91.5, 97.7)	91.1 (87.3, 95.1)
24-month estimate, % (95% CI)	88.6 (84.2, 93)	63.7 (57, 70.4)
Response rate		
ORR, % (95% CI)	85 (79.2, 89.2)	71 (64.8, 77.2)
CR+CRi, %	50	23
PR, %	35	48
Time to next anti-leukaemic therapy		
Number of events (%)	27 (13)	45 (21)
Median, months	Not reached	Not reached
Hazard ratio (95% CI)	0.6 (0.37, 0.97)	

CI = confidence interval; CR = complete response; CRi = complete response with incomplete marrow recovery; INV = investigator; IRC = independent review committee; MRD = minimal residual disease; ORR = overall response rate (CR + CRi + nPR + PR); PR = partial response; HR = hazard ratio.

Figure 1. Kaplan-Meier Curve of Investigator-Assessed Progression-Free Survival (ITT Population) in CLL14



Minimal residual disease (MRD) was evaluated using allele-specific oligonucleotide polymerase chain reaction (ASO-PCR). The cutoff for a negative status was <1 CLL cell per 10^4 leukocytes. Rates of MRD negativity regardless of response and in patients with CR/CRi are shown in Table 16.

Table 16: Minimal Residual Disease Negativity Rates Three Months After the Completion of Treatment in CLL14

	VENCLEXTA + Obinutuzumab (N = 216)	**Obinutuzumab + Chlorambucil (N = 216)**
Peripheral Blood		
MRD negativity rate, n (%)	163 (76)	76 (35)
[95% CI]	[69.17, 81.05]	[28.83, 41.95]
p-value	<0.0001	
MRD negativity rate in patients with CR/CRi, n (%)	91 (42)	31 (14)
[95% CI]	[35.46, 49.02]	[9.96, 19.75]
p-value	<0.0001	
Bone Marrow		
MRD negativity rate, n (%)	123 (57)	37 (17)
[95% CI]	[50.05, 63.64]	[12.36, 22.83]
p-value	<0.0001	
MRD negativity rate in patients with CR/CRi, n (%)	73 (34)	23 (11)
[95% CI]	[27.52, 40.53]	[6.87, 15.55]
p-value	<0.0001	
CI = confidence interval; CR = complete response		

In paired samples, the concordance of MRD negativity between peripheral blood and bone marrow samples at end of treatment was 91% in the venetoclax + obinutuzumab arm and 58% in the obinutuzumab + chlorambucil arm.

The PFS benefit with venetoclax + obinutuzumab versus obinutuzumab + chlorambucil treatment was observed across the following subgroups: sex; age (< 65, ≥65; < 75, ≥75); Binet stage at screening (A,

B, C); estimated CrCL (<70 mL/min, ≥ 70 mL/min); deletion(17p)/*TP53* mutation (yes, no); *IGVH* mutational status (mutated, unmutated).

Patient-Reported Outcomes

Health-Related Quality of Life (HRQoL) was evaluated using the M. D. Anderson Symptom Inventory (MDASI)-CLL and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). Patients receiving venetoclax + obinutuzumab and obinutuzumab + chlorambucil reported no impairment from baseline in physical functioning, role functioning, and global health status/quality of life during treatment and follow-up per the EORTC QLQ-C30, and no increase in symptom burden and interference per the MDASI-CLL. The HRQoL was maintained in both arms with no increase in symptom burden or worsening observed in any quality of life domains.

Study GP28331

Study GP28331 was a multicentre, open-label, non-randomised study of venetoclax administered in combination with obinutuzumab that included 32 patients with previously untreated CLL. The median follow-up in the study was 27 months (range: 16 to 39 months). Twenty-two patients had a baseline creatinine clearance ≥70 mL/min and a baseline ECOG of 0 or 1, and were therefore eligible to receive chemo-immunotherapy (e.g. FCR or BR) as treatment. For these 22 patients, the median age was 62 years (range: 47 to 68 years), 68% were male, and 50% had ECOG score of 1. Key efficacy results were consistent with those observed in CLL14. The overall response rate was 100%, with 73% (16/22) of patients achieving a CR/CRi (investigator-assessed). Median duration of response was not reached (range: 10 to 33 months). The 12-month PFS rate was 100% (95%CI: 100.0 to 100.0) and the 24-month PFS rate was 86% (95%CI: 72.02 to 100.00). After ≥3 months from the last venetoclax dose, 68% (15/22) of patients were MRD negative ($<10^{-4}$) in peripheral blood, assessed using flow cytometry.

VENCLEXTA in Combination with Rituximab

MURANO (Study GO28667)

MURANO was a randomised (1:1), multicentre, open label phase 3 study that evaluated the efficacy and safety of VENCLEXTA in combination with rituximab versus bendamustine in combination with rituximab in patients with CLL who had received at least one line of prior therapy. Patients in the venetoclax + rituximab arm completed the 5-week dose titration schedule (see section 4.2) and received 400 mg VENCLEXTA daily for 2 years from Cycle 1 Day 1 of rituximab in the absence of disease progression or unacceptable toxicity. Rituximab was initiated after the 5-week dose titration at 375 mg/m^2 for Cycle 1 and 500 mg/m^2 for Cycles 2-6. Each cycle was 28 days. Patients randomised to bendamustine + rituximab received bendamustine at 70 mg/m^2 on Days 1 and 2 for 6 cycles and rituximab at the above described dose and schedule. Following completion of 24 months of venetoclax + rituximab regimen, patients continued to be followed for disease progression and overall survival.

A total of 389 patients were randomised; 194 to the venetoclax + rituximab arm and 195 to the bendamustine + rituximab arm. Table 17 shows the baseline demographic and disease characteristics were similar between the venetoclax + rituximab and bendamustine + rituximab arms.

Table 17. Demographics and Baseline Characteristics in MURANO

Characteristic	VENCLEXTA + Rituximab (N = 194)	Bendamustine + Rituximab (N = 195)
Age, years; median (range)	64.5 (28-83)	66 (22-85)
White; %	96.8	96.7
Male; %	70.1	77.4
ECOG performance status; %		
0	57.2	55.7
1	42.3	43.3
2	0.5	1.0
Tumour burden; %		
Absolute lymphocyte count ≥25 x 10^9/L	66.5	68.7
One or more nodes ≥5 cm	45.7	47.6
Number of prior lines of therapy; %		
Median number (range)	1 (1 – 5)	1 (1 – 4)
1	57.2	60.0
2	29.4	22.1
≥3	13.4	17.9
Previous CLL regimens		
Median number (range)	1 (1-5)	1 (1-4)
Prior alkylating agents, %	93.3	95.4
Prior purine analogs, %	80.5	81.4
Prior anti-CD20 antibodies, %	76.3	78.6
Prior B-cell receptor pathway inhibitors, %	1.5	2.6
FCR, %	54.1	55.4
Fludarabine refractory, %	14.1	15.5
CLL subsets %		
17p deletion	26.6	27.2
11q deletion	35.3	37.9
TP53 mutation	25.0	27.7
IgVH unmutated	68.3	68.3
Time since diagnosis, years; median (range)	6.44 (0.5 – 28.4)	7.11 (0.3 -29.5)
FCR = fludarabine, cyclophosphamide, rituximab		

The median survival follow-up at the time of analysis was 23.8 months (range: 0.0 to 37.4 months).

The primary endpoint was progression-free survival (PFS) as assessed by investigators using the International Workshop for Chronic Lymphocytic Leukaemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008).

Efficacy results for MURANO are shown in Table 18. The Kaplan-Meier curves for PFS and overall survival (OS) are shown in Figures 2 and 3, respectively.

Table 18. Efficacy Results for MURANO

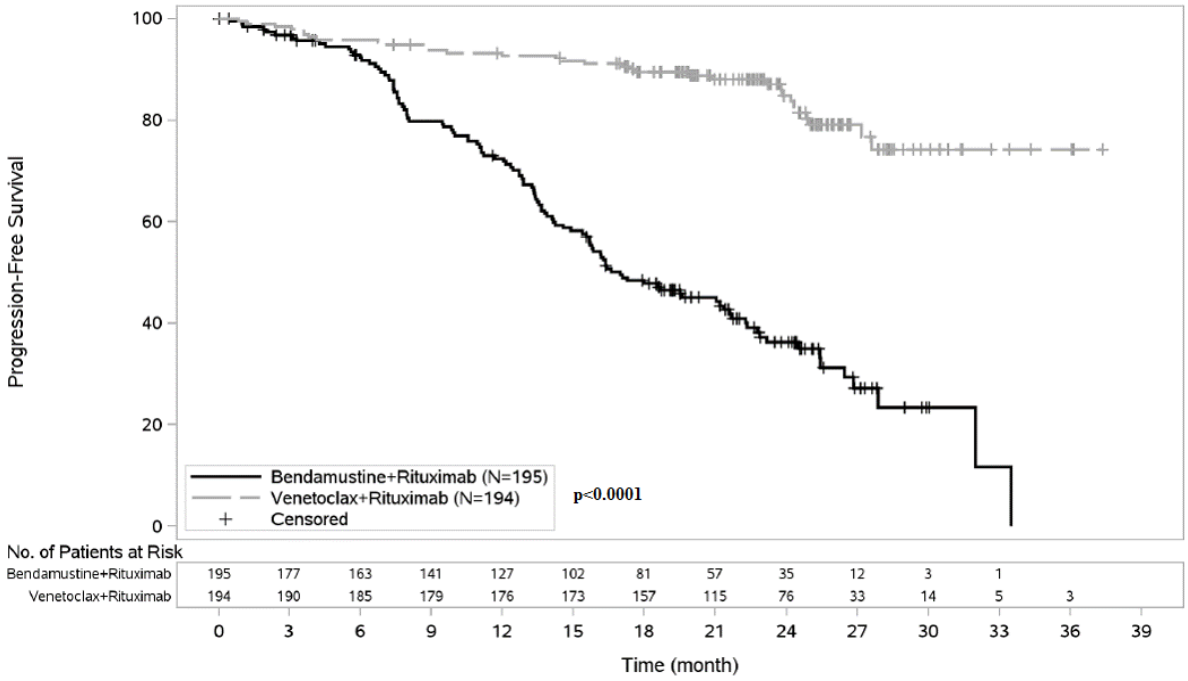
	INV Assessed		IRC Assessed	
	VENCLEXTA + Rituximab (N = 194)	**Bendamustine + Rituximab (N = 195)**	**VENCLEXTA + Rituximab (N = 194)**	**Bendamustine + Rituximab (N = 195)**
Progression-free survival				
Number of events (%)	32 (16.5)	114 (58.5)	35 (18.0)	106 (54.4)
Disease progression	21	98	26	91
Death events	11	16	9	15
Median, months (95% CI)	Not reached	17.0 (15.5, 21.6)	Not reached	18.1 (15.8, 22.3)
HR (95% CI)	0.17 (0.11, 0.25)		0.19 (0.13, 0.28)	
p-value[a]	p < 0.0001		p < 0.0001	
12-month estimate, % (95% CI)	92.7 (89.1, 96.4)	72.5 (65.9, 79.1)	91.2 (87.2, 95.2)	74.1 (67.6, 80.7)
24-month estimate, % (95% CI)	84.9 (79.1, 90.6)	36.3 (28.5, 44.0)	82.8 (76.6, 88.9)	37.4 (29.4, 45.4)
Response rate				
ORR, % (95% CI)	93.3 (88.8, 96.4)	67.7 (60.6, 74.2)	92.3 (87.6, 95.6)	72.3 (65.5, 78.5)
CR+CRi, (%)	26.8	8.2	8.2[b]	3.6[b]
nPR, (%)	3.1	6.2	1.5	0.5
PR, (%)	63.4	53.3	82.5	68.2
Overall survival				
Number of deaths (%)	15 (7.7)	27 (13.8)	NA	NA
Hazard Ratio (95% CI)	0.48 (0.25, 0.90)		NA	
Time to next anti-leukaemic therapy				
Number of events (%)	23 (11.9)	83 (42.6)	NA	NA
Median, months	Not reached	26.4	NA	NA
Hazard ratio (95% CI)	0.19 (0.12, 0.31)		NA	
Event-free survival				
Number of events (%)	33 (17.0)	118 (60.5)	NA	NA
Median, months	Not reached	16.4	NA	NA
Hazard ratio (95% CI)	0.17 (0.11, 0.25)		NA	

CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery; INV = investigator; IRC = independent review committee; MRD = minimal residual disease; NA = not available; nPR = nodular partial remission; ORR = overall response rate (CR + CRi + nPR + PR); PR = partial remission; HR = hazard ratio.

[a]Stratified log-rank test.

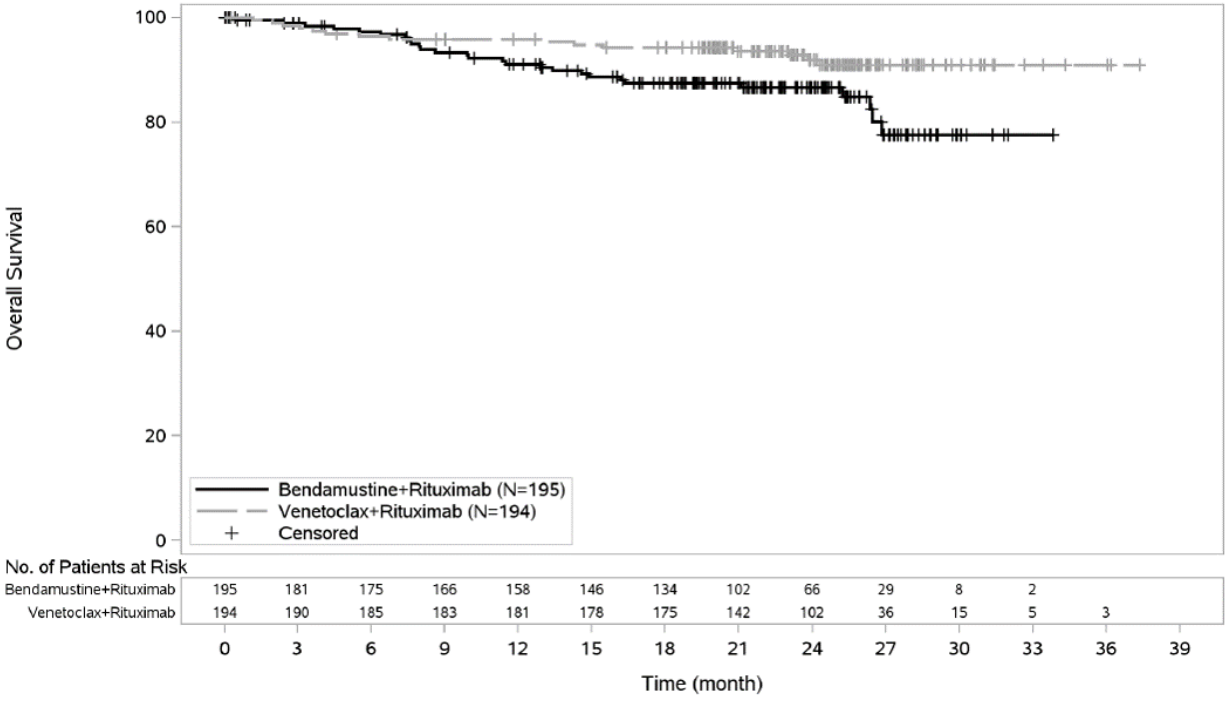
[b]The discrepancy between IRC- and investigator-assessed CR rate was primarily due to interpretation of residual adenopathy on CT scans. Eighteen patients in the venetoclax + rituximab arm and 3 patients in the bendamustine + rituximab arm had negative bone marrow and lymph nodes <2 cm.

Figure 2. Kaplan-Meier curve of Investigator assessed progression-free survival (ITT Population) in MURANO



At the time of primary analysis (data cutoff date 8 May 2017), 65 patients completed the 24 month venetoclax + rituximab treatment regimen without progression and 78 patients were still receiving venetoclax (+18 months of treatment). Of the 65 patients who remained progression free at 24 months, only 2 patients progressed after treatment completion. Twelve patients had a 3-month follow-up visit and remained progression free. Of the 12 patients, 5 were also assessed at 6-month follow-up and remained progression free.

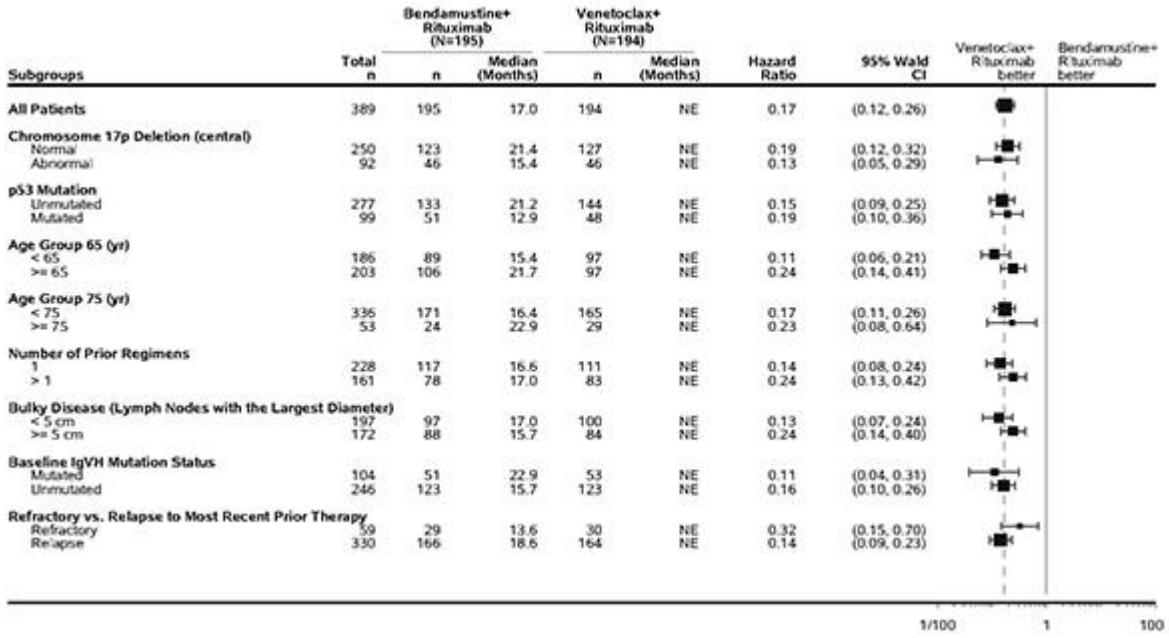
Figure 3. Kaplan-Meier Curve of Overall Survival (ITT Population) in MURANO



Minimal residual disease was evaluated using ASO-PCR and flow cytometry. The cutoff for a negative status was one CLL cell per 10^4 leukocytes. MRD data were available in peripheral blood in nearly all patients (187/194 in the venetoclax + rituximab arm versus 179/195 in the bendamustine + rituximab arm) and in a subset of patients for bone marrow (74/194 in the venetoclax + rituximab arm versus 41/195 in the bendamustine + rituximab arm). Peripheral blood MRD negativity rates, assessed at any time during the study, were observed in 84% (162/194) of patients in the venetoclax + rituximab arm versus 23% (45/195) of patients in the bendamustine + rituximab arm. Bone marrow MRD negativity rates were 27.3% (53/194 patients) in the venetoclax + rituximab arm versus 1.5% (3/195 patients) in the bendamustine + rituximab arm. At the 9-month response assessment, MRD negativity in the peripheral blood was 62.4% in the venetoclax + rituximab arm versus 13.3% in the bendamustine + rituximab arm and this rate was maintained in the venetoclax + rituximab arm for at least an additional 9 months (59.8% in venetoclax + rituximab versus 5.1% in bendamustine + rituximab), the last visit for which complete data were available prior to the clinical cutoff date.

The PFS benefit with venetoclax + rituximab versus bendamustine + rituximab treatment was observed across all subgroups examined. Progression-free analyses by pre-specified subgroups are shown in Figure 4.

Figure 4. Forest Plot of Investigator-Assessed PFS in Subgroups from MURANO



17p deletion status was determined based on central laboratory test results.
Unstratified hazard ratio is displayed on the X-axis with logarithmic scale.
NE = not evaluable

VENCLEXTA as Monotherapy

The safety and efficacy of VENCLEXTA were established in open-label, multicentre clinical trials of patients with CLL or SLL who had received at least one prior therapy, including those with deletion of the p13 locus on chromosome 17 (17p deletion).

Study M13-982

Study M13-982 was a multicentre, single-arm open-label trial of 107 patients with previously treated CLL with 17p deletion. Table 19 summarises the baseline demographic and disease characteristics of the study population.

Table 19. Baseline Patient Characteristics in Study M13-982

Characteristic	N = 107[a]
Age, years; median (range)	67 (37-85)
White; %	97.2
Male; %	65.4
ECOG performance status; % 0 1 2	 39.3 52.3 8.4
Tumour burden; % Absolute lymphocyte count ≥25 x 10^9/L One or more nodes ≥5 cm	 50.5 53.3
Number of prior therapies; median (range)	2 (1-10)
Time since diagnosis, years; median (range)[b]	6.8 (0.1-32)
[a]One patient did not harbour the 17p deletion. [b]N=106.	

Among the patients, 37.4% (34/91) were fludarabine refractory, 81.1% (30/37) had unmutated *IGHV*, and 23.8% (19/80) had 11q deletion.

Patients received VENCLEXTA via a weekly dose titration schedule starting at 20 mg and titrating to 50 mg, 100 mg, 200 mg and finally 400 mg once daily. Patients continued to receive 400 mg of VENCLEXTA orally once daily until disease progression or unacceptable toxicity. The median time on treatment at the time of evaluation was 12.1 months (range: 0 to 21.5 months).

The primary efficacy endpoint was overall response rate (ORR) as assessed by an Independent Review Committee (IRC) using the International Workshop for Chronic Lymphocytic Leukaemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008). Efficacy results for Study M13-982 are shown in Table 20.

Table 20. Efficacy Results in Study M13-982

	IRC Assessment (N=107)[a]	Investigator Assessment (N=107)[a]
ORR, % (95% CI)	79.4 (70.5, 86.6)	73.8 (64.4, 81.9)
CR + CRi (%)	7.5	15.9
nPR (%)	2.8	3.7
PR (%)	69.2	54.2
DOR, % (95% CI) 12-month estimate	84.7 (74.5, 91.0)	89.1 (79.2, 94.4)

[a]One patient did not harbour the 17p deletion.
CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery; DOR = duration of response; IRC = independent review committee; nPR = nodular partial remission; ORR = overall response rate (CR + CRi + nPR + PR); PR = partial remission.

Based on a later data cutoff date (15 June 2017), which included an additional 51 patients enrolled in a safety expansion cohort, and investigator-assessed efficacy (N=158), the median duration of response (DOR) was 36.2 months (95% CI: 27.2, NA). The median duration of progression-free survival (mPFS) was 28.2 months (95% CI: 23.4, 37.0).

Minimal residual disease was evaluated using flow cytometry in 45 of 107 patients who achieved complete remission (CR), complete remission with incomplete marrow recovery (Cri), or partial remission (PR) with limited remaining disease with VENCLEXTA treatment. The cut-off for a negative status was one CLL cell per 10^4 leukocytes in the sample (i.e., an MRD value of $<10^{-4}$ was considered MRD negative). Seventeen percent (18/107) of patients were MRD negative in the peripheral blood, including six patients who were also MRD negative in the bone marrow.

There were 73 patients who completed the Global Health Status assessment (GHS) and 76 patients who completed both the Emotional (EF) and Social Functioning (SF) assessments in the EORTC QLQ-C30 questionnaire at both baseline and week 24. There were 74 and 77 patients, respectively, who completed the Role functioning (RF) and the Fatigue symptom scale assessments at both baseline and week 24. Following treatment with VENCLEXTA, patients showed improvement in GHS (16%), EF (10.6%), SF (17.1%), RF (16.2%), and the Fatigue symptom score (17.5%) at week 24. Improvements in these measures were seen as early as week 4.

Study M12-175

Study M12-175 was a multicentre, open-label trial that enrolled patients with previously treated CLL or SLL, including those with 17p deletion. Efficacy was evaluated in 67 patients (59 with CLL, 8 with SLL) who had received a daily dose of 400 mg of VENCLEXTA following a dose titration schedule.

Patients continued to receive 400 mg of VENCLEXTA monotherapy orally once daily until disease progression or unacceptable toxicity. The median time on treatment at the time of evaluation was 11.5 months (range: 22.1 to 50.1 months). Table 21 summarises the baseline demographic and disease characteristics of the study population.

Table 21. Baseline Patient Characteristics of Evaluable Patients in Study M12-175

Characteristic	N=67
Age, years; median (range)	66 (42-84)
White; %	86.6
Male; %	77.6
ECOG performance status[a]; % 0 1 2	 47.7 52.3 0
Tumour burden; % Absolute lymphocyte count ≥25 x 10^9/L One or more nodes ≥5 cm	 29.9 66.7
Number of prior therapies; median (range)	3 (1-11)
Time since diagnosis, years; median (range)	9 (1.1-27.3)
[a]Missing for two patients.	

Among the patients, 70.1% were fludarabine refractory, 66.7% (22/33) had unmutated *IGHV*, 31.0% (18/58) had 11q deletion, and 24.1% (14/58) had 17p deletion.

Overall response rate and duration of response were evaluated by both investigators and an IRC using the IWCLL updated NCI-WG guidelines (2008). Efficacy results are shown in Table 22:

Table 22. Efficacy Results in Study M12-175

	IRC Assessment N=57	Investigator Assessment N=67
ORR, % (95% CI)	73.7 (60.3, 84.5)	82.1 (70.8, 90.4)
CR + CRi (%)	7.0	13.4
nPR (%)	0	3.0
PR (%)	66.7	65.7
DOR, % (95% CI) 12-month estimate	88.8 (67.5, 96.5)	92.1 (80.2, 96.9)
CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery; DOR = duration of response; IRC = independent review committee; nPR = nodular partial remission; ORR = overall response rate (CR + CRi + nPR + PR); PR = partial remission.		

For the 8 patients with SLL, the investigator-assessed ORR was 100%.

Study M14-032

Study M14-032 was an open label, multicentre, study that evaluated the efficacy of VENCLEXTA in patients with CLL who had been previously treated with and progressed on or after ibrutinib (Arm A) or idelalisib (Arm B). Patients received a daily dose of 400 mg of VENCLEXTA following the dose-titration schedule. Patients continued to receive VENCLEXTA 400 mg once daily until disease progression or unacceptable toxicity was observed.

Efficacy was evaluated by investigators and an IRC according to IWCLL updated NCI WG guidelines (2008). Response assessments were performed at 8 weeks, 24 weeks, and every 12 weeks thereafter for the 64 patients in the main cohort, while the patients enrolled in the expansion had disease assessment at weeks 12 and 36.

A total of 127 patients were enrolled in the study, which included 64 patients in the main cohort (43 with prior ibrutinib, 21 with prior idelalisib) and 63 patients in an expansion cohort (48 with prior

ibrutinib, 15 with prior idelalisib). Table 23 summarises the baseline demographic and disease characteristics of the study population.

Table 23. Baseline Patient Characteristics of Evaluable Patients in Study M14-032

Characteristic	N=127
Age, years; median (range)	66 (28-85)
White; %	92
Male; %	70
Tumour burden; % Absolute lymphocyte count ≥25 x 10^9/L One or more nodes ≥5 cm	 31 41
Number of prior therapies; median (range)	4 (1 to 15)
Time since diagnosis, years; median (range)	8.3 (0.3-18.5)[a]
[a] N = 96	

Efficacy data are presented with data cutoff date of 26 July 2017. Investigator-assessment of disease responses to venetoclax treatment are available for all 127 subjects (64 in the main cohort and 63in the expansion cohort). The IRC assessments of disease responses are available for 123 of the 127 subjects. Efficacy results for 127 patients assessed by investigator and 127 patients assessed by IRC at the same time points are shown in Table 24.

Table 24. Efficacy Results in Study M14-032

	IRC Assessment N=127[a]	Investigator Assessment N=127
ORR, % (95% CI)	70.1 (61.3, 77.9)	63.0 (54.0, 71.4)
CR + CRi (%)	0.8	8.7
nPR (%)	0	2.4
PR (%)	69.3	52.0
DOR, % (95% CI) 6-month estimate 12-month estimate	N=89 97.4 (90.0, 99.4) NA	N=83 96.2 (88.7, 98.8) 87.6 (77.4, 93.3)
Time to first response, median, months (range)	2.5 (1.0-8.9)	2.5 (1.6, 14.9)
[a] Not assessed N=4 CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery; DOR = duration of response; IRC = independent review committee; nPR = nodular partial remission; ORR = overall response rate (CR + CRi + nPR + PR); PR = partial remission.		

The median duration of treatment with VENCLEXTA for 127 patients was 14.3 months (range: 0.1 to 31.4 months).

The MRD negativity rate in peripheral blood for all 127 patients was 25.2% (32/127), including 8 patients who achieved MRD negativity in bone marrow.

Acute Myeloid Leukaemia

VENCLEXTA in Combination with Azacitidine

VIALE-A

VIALE-A was a randomised (2:1), double-blind, placebo controlled phase 3 study that evaluated the efficacy and safety of VENCLEXTA in combination with azacitidine versus placebo in combination with azacitidine in patients with newly diagnosed AML who were ineligible for intensive chemotherapy.

Patients in VIALE-A completed the 3-day dose titration phase to a final 400 mg once daily dose during the first cycle of treatment (see section 4.2) and received VENCLEXTA 400 mg orally once daily on Days 1-28, plus azacitidine 75 mg/m^2 either intravenously or subcutaneously, on Days 1-7 of each 28-day cycle, beginning on Cycle 1 Day 1. During the dose titration phase, patients received TLS prophylaxis and were hospitalised for monitoring. Once bone marrow assessment confirmed a remission, defined as less than 5% leukaemia blasts with cytopenia following Cycle 1 treatment, VENCLEXTA or placebo was interrupted up to 14 days or until ANC ≥500/microliter and platelet count $\geq 50 \times 10^3$/microliter. Azacitidine was resumed on the same day as VENCLEXTA or placebo following interruption (see section 4.2 **Dose Modifications Based on Toxicities**). Azacitidine dose reduction was implemented in the clinical trial for management of haematological toxicity. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity.

A total of 431 patients were randomised: 286 to the venetoclax + azacitidine arm and 145 to the placebo + azacitidine arm. The baseline demographic and disease characteristic are shown in Table 25.

Table 25. Baseline Demographic and Disease Characteristics in Patients with AML in VIALE-A

Characteristic	VENCLEXTA + Azacitidine (N = 286)	Placebo + Azacitidine (N = 145)
Age, years; median (range)	76 (49-91)	76 (60-90)
Race		
White; %	76	75
Males; %	60	60
ECOG performance status; % 0-1 2 3	 55 40 5.6	 56 41 3.4
Bone marrow blast; % <30% ≥30% to <50% ≥50%	 30 21 49	 28 23 49
Disease history; % *De Novo* AML Secondary AML	 75 25	 76 24
Cytogenetic risk detected[a] %		
Intermediate	64	61
Poor	36	39
Mutation analyses detected; n/N[b] (%)		
IDH1 or IDH2 [c,d]	61/245 (25)	28/127 (22)
IDH1[c]	23/245 (9.4)	11/127 (8.7)
IDH2[d]	40/245 (16)	18/127 (14)
FLT3[e]	29/206 (14)	22/108 (20)
NPM1[f]	27/163 (17)	17/86 (20)
TP53[f]	38/163 (23)	14/86 (16)

[a]Per the 2016 National Comprehensive Cancer Network (NCCN) Guidelines.
[b]Number of evaluable BMA specimens received at baseline.
[c]Detected by Abbott RealTi*me* IDH1 assay.
[d]Detected by Abbott RealTi*me* IDH2 assay.
[e]Detected by LeukoStrat® CDx FLT3 mutation assay.
[f]Detected by MyAML® assay.

The dual primary endpoints of the study were overall survival (OS) measured from the date of randomisation to death from any cause and composite complete remission rate (complete remission + complete remission with incomplete blood count recovery; CR+CRi). The overall median follow-up at the time of analysis was approximately 20.5 months (range: <0.1 to 30.7 months).

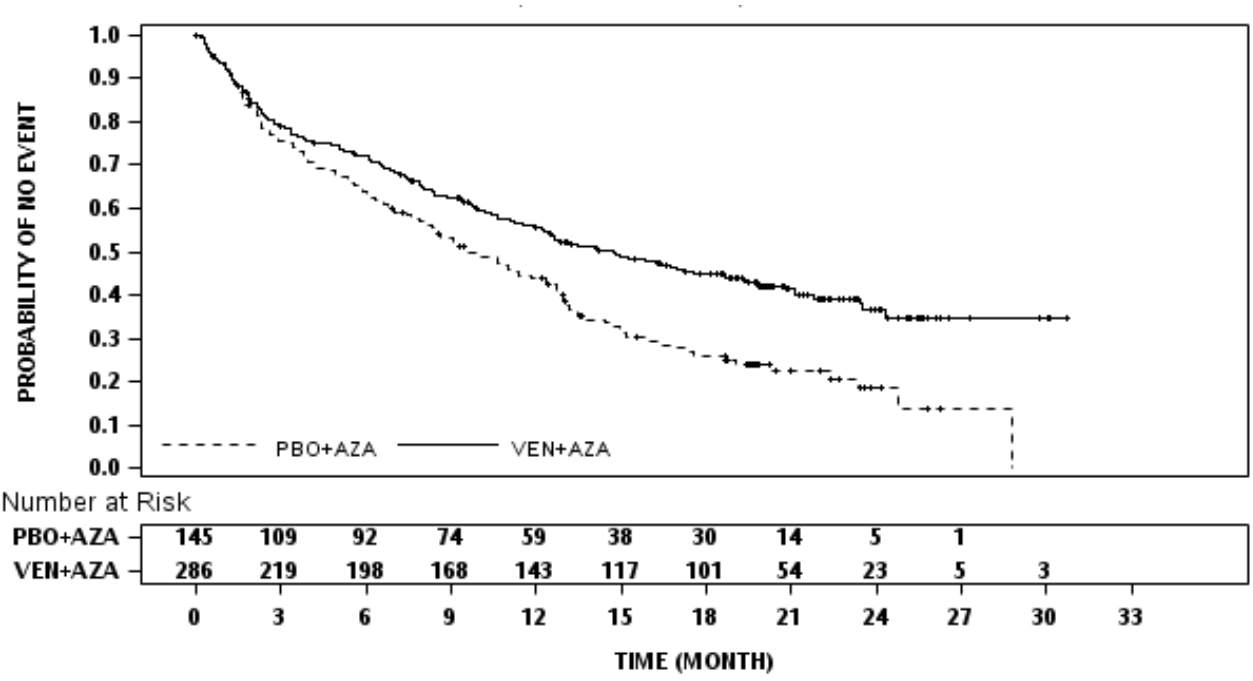
Venetoclax + azacitidine demonstrated 34% reduction in the risk of death compared with placebo + azacitidine (p <0.001). The efficacy results are presented in Table 26 and Table 27. The Kaplan-Meier curve for OS is shown in Figure 5.

Table 26. Overall Survival at Time of Second Interim Analysis (data cutoff date 4 January 2020) and Composite Complete Remission Rate at Time of First Interim Analysis (data cutoff date 1 October 2018) in Patients with Newly-Diagnosed AML in VIALE-A

Endpoint	VENCLEXTA + Azacitidine	Placebo + Azacitidine
Overall survival	**(N=286)**	**(N=145)**
Number of deaths, n (%) Median[a] survival, months (95% CI)	161 (56) 14.7 (11.9, 18.7)	109 (75) 9.6 (7.4, 12.7)
Hazard ratio[b] (95% CI)	0.66 (0.52, 0.85)	
p-value[b]	<0.001	
CR + CRi[c]	**(N=147)**	**(N=79)**
n (%) (95% CI)	96 (65) (57, 73)	20 (25) (16, 36)
p-value[d]	<0.001	

CI = confidence interval.
CR (complete remission) was defined as absolute neutrophil count >1,000/microliter, platelets >100,000/microliter, red blood cell transfusion independence, and bone marrow with <5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; CRi = complete remission with incomplete blood count recovery.
[a]Kaplan-Meier estimate.
[b]Hazard ratio estimate (venetoclax +azacitidine vs placebo + azacitidine) is based on Cox-proportional hazards model stratified by cytogenetics (intermediate risk, poor risk) and age (18 - <75 years, ≥75 years) as assigned at randomisation; P-value based on log-rank test stratified by the same factors.
[c]The CRi+CRi rate is from a planned interim analysis of first 226 patients randomised with 6 months of follow-up.
[d]P-value is from Cochran-Mantel-Haenszel test stratified by cytogenetics (intermediate risk, poor risk) and age (18 - <75 years, ≥75 years).

Figure 5: Kaplan-Meier Curve for Overall Survival in VIALE-A



Key secondary efficacy endpoints are presented in Table 27 below.

Table 27. Additional Efficacy Endpoints in VIALE-A

Endpoint	VENCLEXTA + Azacitidine (N = 286)	Placebo + Azacitidine (N = 145)
CR, n (%) (95% CI)	105 (37) (31, 43)	26 (18) (12, 25)
p-value[a]	<0.001	
Median DOR[b] (months)	17.5	13.3
(95% CI)	(15.3, NE)	(8.5, 17.6)
CR+CRh, n (%) (95% CI)	185 (65) (59, 70)	33 (23) (16, 31)
p-value[a]	<0.001	
Median DOR[b] (months)	17.8	13.9
(95% CI)	(15.3, NE)	(10.4, 15.7)
CR+CRi, n (%) (95% CI) Median DOR[b] (months) (95% CI)	190 (66) (61, 72) 17.5 (13.6, NE)	41 (28) (21, 36) 13.4 (5.8, 15.5)
CR+CRh rate by initiation of Cycle 2, n (%) (95% CI)	114 (40) (34, 46)	8 (6) (2, 11)
p-value[a]	<0.001	
CR+CRi rate by initiation of Cycle 2, n (%) (95% CI)	124 (43) (38, 49)	11 (8) (4, 13)
p-value[a]	<0.001	
CR+CRh rate in *FLT3* subgroup, n/N (%) (95% CI)	19/29 (66) (46, 82)	4/22 (18) (5, 40)
p-value[c]	0.001	
CR+CRi rate in *FLT3* subgroup, n/N (%) (95% CI)	21/29 (72) (53, 87)	8/22 (36) (17, 59)
p-value[c]	0.021	
CR+CRh rate in *IDH1/2* subgroup, n/N (%) (95% CI)	44/61 (72) (59, 83)	2/28 (7) (1, 24)
p-value[c]	<0.001	
CR+CRi rate in *IDH1/2* subgroup, n/N (%) (95% CI)	46/61 (75) (63, 86)	3/28 (11) (2, 28)
p-value[c]	<0.001	
OS in *IDH1/IDH2* subgroup Number of deaths, n/N (%) Median OS[d], months (95%CI)	29/61 (48) Not Reached (12.2, Not Estimable)	24/28 (86) 6.2 (2.3, 12.7)
Hazard ratio[e] (95% CI)	0.34 (0.20, 0.60)	
p-value[e]	<0.0001	
Transfusion independence rate platelet, n (%) (95% CI)	196 (69) (63, 74)	72 (50) (41, 58)
p-value[a]	<0.001	
Transfusion independence rate red blood cell, n (%) (95% CI)	171 (60) (54, 66)	51 (35) (27, 44)
p-value[a]	<0.001	

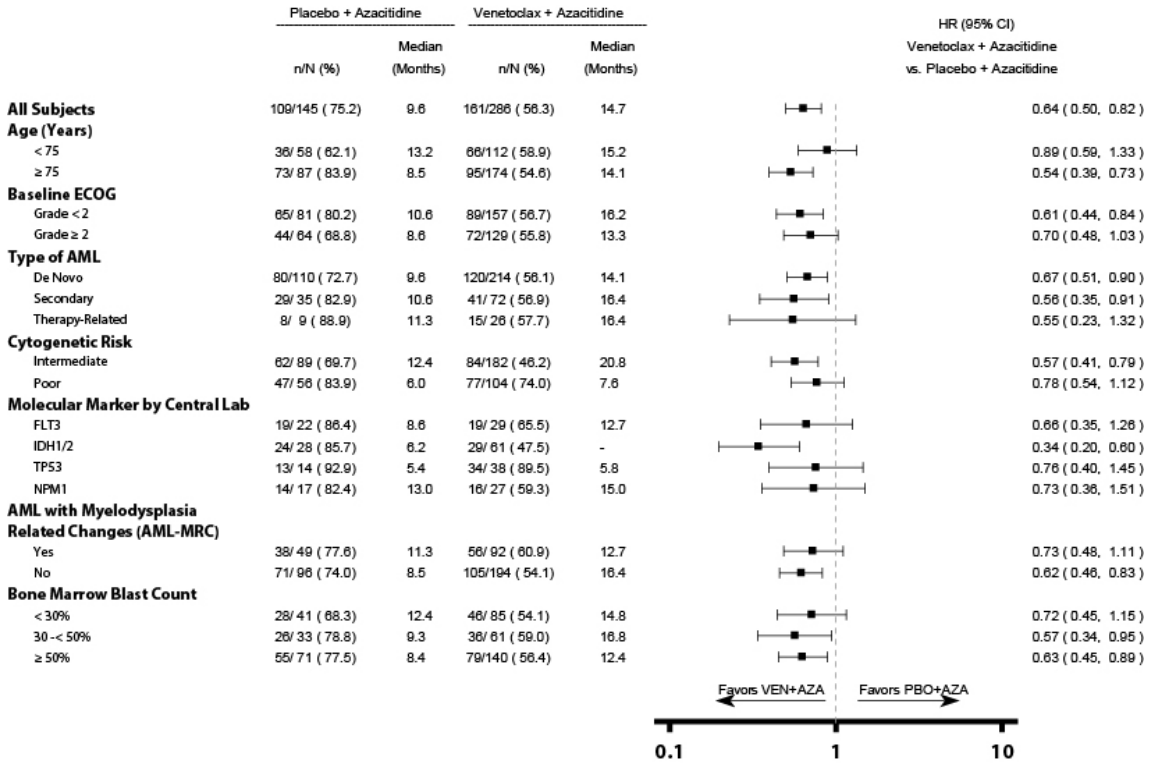
Endpoint	VENCLEXTA + Azacitidine (N = 286)	Placebo + Azacitidine (N = 145)
CR+CRi MRD response rate[f] n (%) (95% CI)	 67 (23) (19, 29)	 11 (8) (4, 13)
p-value[a]	<0.001	
Event-free survival (EFS) Number of EFS events n (%) Median EFS[d], (months) (95% CI)	 191 (67) 9.8 (8.4, 11.8)	 122 (84) 7.0 (5.6, 9.5)
Hazard ratio[g] (95% CI)	0.63 (0.50, 0.80)	
p-value[g]	<0.001	

CI = confidence interval; CR = complete remission; CRh = complete remission with partial haematological recovery; CRi = complete remission with incomplete blood count recovery; NE = not estimable.
CR (complete remission) was defined as absolute neutrophil count >1,000/microliter, platelets >100,000/microliter, red blood cell transfusion independence, and bone marrow with <5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
CR + CRi = complete remission + complete remission with incomplete blood count recovery; DOR = duration of response; FLT = FMS-like tyrosine kinase; IDH = isocitrate dehydrogenase; MRD = minimal/measurable residual disease.
Transfusion independence is defined as a period of at least 56 consecutive days (≥56 days) with no transfusion after the first dose of study drug and on or before the last dose of the study drug +30 days, or before relapse or disease progression or before the initiation of post-treatment therapy whichever is earlier.
CRh (complete remission with partial haematological recovery) was defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter).
[a]P-value is from Cochran-Mantel-Haenszel test stratified by age (18 - <75 years, ≥75 years) and cytogenetic (intermediate risk, poor risk).
[b]DOR (duration of response) was defined as time from first response of CR for DOR of CR, from first response of CR or CRi for DOR of CR+CRi, or from first response of CR or CRh for DOR of CR+CRh, to the first date of confirmed morphologic relapse, confirmed progressive disease or death due to disease progression, whichever occurred earlier. Median DOR from Kaplan-Meier estimate.
[c]P-value is from Fisher's exact test.
[d]Kaplan-Meier estimate.
[e]Hazard ratio estimate (venetoclax + azacitidine vs placebo + azacitidine) is based on unstratified Cox-proportional hazards model. P-value from unstratified log-rank test.
[f]CR+CRi MRD response rate is defined as the % of patients achieving a CR or CRi and demonstrated an MRD response of $<10^{-3}$ blasts in bone marrow as determined by a standardised, central multicolor flow cytometry assay.
[g]Hazard ratio estimate (venetoclax + azacitidine vs placebo + azacitidine) is based on Cox-proportional hazards model stratified by age (18 - <75 years, ≥75) and cytogenetics (intermediate risk, poor risk) as assigned at randomisation; p-value based on log-rank test stratified by the same factors.

Of the patients who were red blood cell transfusion dependent at baseline and treated with venetoclax + azacitidine, 49% (71/144) became transfusion independent. Of the patients who were platelet transfusion dependent at baseline and treated with venetoclax + azacitidine, 50% (34/68) became transfusion independent.

The median time to first response of CR or CRi was 1.3 month (range, 0.6 to 9.9 months) with venetoclax + azacitidine treatment. The median time to best response of CR or CRi was 2.3 month (range, 0.6 to 24.5 months). Overall survival by subgroups are shown in Figure 6.

Figure 6. Forest Plot of Overall Survival by Subgroups from VIALE-A



Unstratified hazard ratio (HR) is displayed on the X-axis with logarithmic scale.
"-" = Not Estimable

Fatigue was assessed by the Patient Reported Outcomes Measurement Information System (PROMIS), Cancer Fatigue Short Form (SF 7a) and health-related quality of life (HRQoL) was assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC QLQ-C30) global health status/ quality of life (GHS/QoL). Patients receiving venetoclax + azacitidine showed no clinically meaningful differences in the mean change from baseline fatigue score as assessed using the PROMIS-SF 7a than patients treated with placebo + azacitidine (-3.036 vs -0.796, -2.263 vs -1.976, -3.377 vs -0.990, -2.209 vs -1.745, and -1.644 vs -1.453 at Cycles 5, 7, 9, 11 and 13, respectively).

Patients treated with venetoclax + azacitidine observed a longer time to deterioration defined as the first event of worsening of at least 10 in the EORTC-QLQ-C30 Global Health Status score (16.5 months; 95% CI: 9.76, not estimable) than patients treated with placebo + azacitidine (9.3 months; 95% CI: 4.67,16.60; p=0.066). Patients receiving venetoclax + azacitidine did not experience meaningful additional fatigue or decrement in HRQoL compared to patients receiving placebo + azacitidine.

M14-358

The efficacy of VENCLEXTA was established in a non-randomised clinical trial of VENCLEXTA in combination with azacitidine (N=84) in newly diagnosed patients with AML who were ineligible for intensive chemotherapy.

Patients received VENCLEXTA via a daily dose titration schedule to a final 400 mg once daily dose. During the dose titration schedule, patients received TLS prophylaxis and were hospitalised for monitoring. Azacitidine at 75 mg/m^2 was administered either intravenously or subcutaneously on Days 1-7 of each 28-day cycle beginning on Cycle 1 Day 1. Once bone marrow assessment confirmed a remission, defined as less than 5% leukaemia blasts with cytopenia following Cycle 1 treatment, VENCLEXTA was interrupted up to 14 days or until ANC ≥500/microliter and platelet count ≥50 ×

10^3/microliter. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Azacitidine dose reduction was implemented in the clinical trial for management of haematological toxicity (see azacitidine full Data Sheet).

Table 28 summarises the baseline demographic and disease characteristics of the study population.

Table 28. Baseline Patient Characteristics for Patients with AML Treated with VENCLEXTA in Combination with Azacitidine (M14-358)

Characteristic	VENCLEXTA + Azacitidine (N = 84)
Age, years; median (range)	74.5 (61-90)
White; %	91
Male; %	61
ECOG performance status; % 0-1 2 3	 69 29 2
Bone marrow blast; % <30% ≥30% - <50% ≥50%	 29 35 37
History of antecedent haematological disorder; %	20
Mutation analyses; % (identified/tested)	
TP53	22 (16/74)
IDH1 or *IDH2*	27 (20/74)
FLT3	15 (11/74)
NPM1	19 (14/74)
Cytogenetic risk[a,b]; %	
Intermediate	60
Poor	39

[a]As defined by the National Comprehensive Cancer Network (NCCN) risk categorisation v2014.
[b]No mitosis in 1 patient (excluded favorable risk by Fluorescence in situ Hybridization [FISH] analysis).

The median follow-up was 28.9 months (range: 0.4 to 42.0 months) for VENCLEXTA in combination with azacitidine. The efficacy results are shown in Tables 29 and 30.

Table 29. Efficacy Results for Newly Diagnosed Patients with AML Treated with VENCLEXTA in Combination with Azacitidine (M14-358)

Endpoint	VENCLEXTA + Azacitidine (N = 84)
CR, n (%) (95% CI) Median DOR[a] (months) (95% CI)	37 (44) (33, 55) 23.5 (15.1, 30.2)
CRi, n (%) (95% CI) Median DOR[a] (months) (95% CI)	23 (27) (18, 38) 10.6 (5.6, NE)
CR+CRi, n (%) (95% CI) Median DOR[a] (months) (95% CI)	60 (71) (61, 81) 21.9 (15.1, 30.2)
CRh, n (%) (95% CI) Median DOR[a] (months) (95% CI)	17 (20) (12, 30) 7.9 (5.8, NE)
CR+CRh, n (%) (95% CI) Median DOR[a] (months) (95% CI)	54 (64) (53, 74) 21.7 (14.6, 30.3)
Transfusion independence rate, n/N (%) Red blood cell[b] Platelet[c]	 26/51 (51) 16/27 (59)

CI = confidence interval; NE = not estimable.
CR (complete remission) was defined as absolute neutrophil count ≥1,000/microliter, platelets ≥100,000/microliter, red blood cell transfusion independence, and bone marrow with <5% blasts.
Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
CRh (complete remission with partial haematological recovery) was defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter).
CRi (complete remission with incomplete blood count recovery) was defined the same as all of the criteria for CR except for residual neutropenia <1,000/microliter or thrombocytopenia <100,000/microliter.
[a]DOR (duration of response) was defined as time from first response of CR for DOR of CR, or from first response of CRi for DOR of CRi, or from first response of CR or CRi for DOR of CR+CRi, or from first response of CRh for DOR of CRh, or from first response of CR+CRh for DOR of CR+CRh, to the first date of relapse, clinical disease progression, or death due to disease progression, whichever occurred earlier. Median DOR from Kaplan-Meier estimate.
[b]Evaluated for patients who were dependent at baseline for red blood cell transfusion.
[c]Evaluated for patients who were dependent at baseline for platelet transfusion.

Table 30. Time to Response in Patients with AML Treated with VENCLEXTA in Combination with Azacitidine (M14-358)

Endpoint	VENCLEXTA in Combination with Azacitidine (N = 84)
Median time to BEST response of CR (months) Range (months)	2.1 (0.7 – 10.9)
Median time to FIRST response of CR+CRh (months) Range (months)	1.0 (0.7 – 8.9)
Median time to FIRST response of CR+CRi (months) Range (months)	1.2 (0.7 – 7.7)

Median overall survival for patients treated with VENCLEXTA in combination with azacitidine was 16.4 months (95% CI: 11.3, 24.5).

Remissions (CR or CRh) were observed across subgroups with different baseline characteristics. For patients with poor or intermediate risk cytogenetics similar remission rates were observed, the rates were 58% or 70%, respectively. For patients with the following identified mutations, the remissions were as follows: *TP53*: 56% (9/16), *IDH1 / 2*: 75% (15/20), *FLT3*: 64% (7/11) and *NPM1*: 71% (10/14).

Remissions (CR or CRi) were observed across subgroups with different baseline characteristics. For patients with poor or intermediate risk cytogenetics similar remission rates were observed, the rates were 67% or 76%, respectively. For patients with the following identified mutations, the remissions were as follows: *TP53*: 56% (9/16), *IDH1 / 2*: 90% (18/20), *FLT3*: 64% (7/11) and *NPM1*: 79% (11/14).

Minimal residual disease was evaluated from bone marrow aspirate specimens for patients who achieved CR or CRh following treatment with VENCLEXTA in combination with azacitidine. Of those patients, 52% (28/54) achieved MRD less than one AML cell per 10^3 leukocytes in the bone marrow.

Minimal residual disease was evaluated from bone marrow aspirate specimens for patients who achieved CR or CRi following treatment with VENCLEXTA in combination with azacitidine. Of those patients, 48% (29/60) achieved MRD less than one AML cell per 10^3 leukocytes in the bone marrow.

Of patients treated with VENCLEXTA in combination with azacitidine, 18% (15/84) achieved a CR/CRi and subsequently received stem cell transplant.

VENCLEXTA in Combination with Low-Dose Cytarabine

VIALE-C

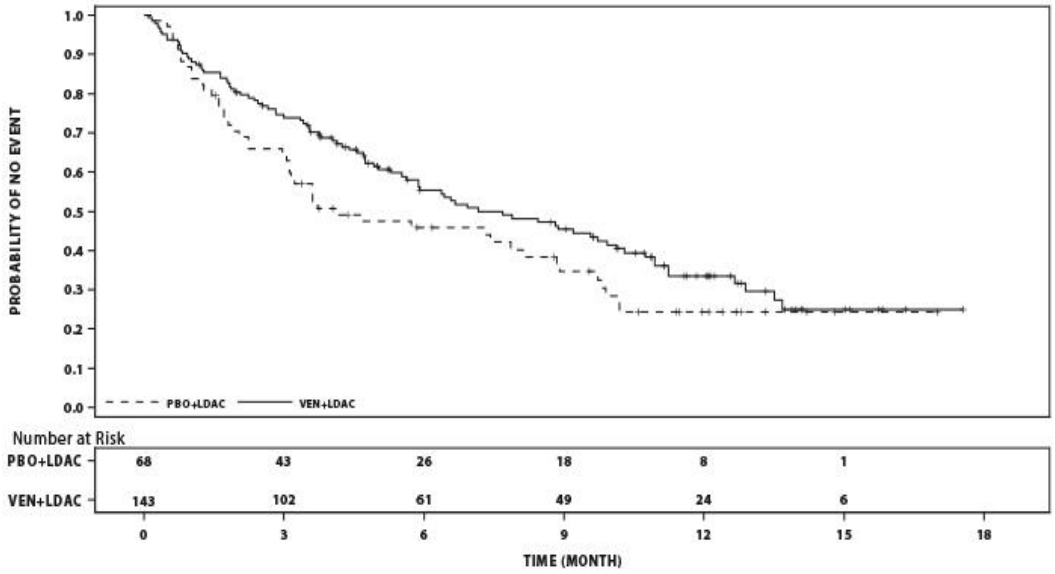
The efficacy and safety of VENCLEXTA in 211 patients with newly diagnosed AML were evaluated in a randomised (2:1), double-blind, placebo controlled, multi-centre study (VIALE-C).

Patients in VIALE-C completed the 4-day dose titration schedule to a final 600 mg once daily dose during the first cycle of treatment (see section 4.2) and received VENCLEXTA 600 mg orally once daily on Days 1-28, plus cytarabine 20 mg/m^2 subcutaneously, once daily on Days 1-10. Once daily oral placebo was administered on Days 1-28 plus cytarabine 20 mg/m^2 subcutaneously once daily on Days 1-10. Once bone marrow assessment confirmed a remission, defined as less than 5% leukaemia blasts with cytopenia following Cycle 1 treatment, VENCLEXTA or placebo was interrupted up to 14 days or until ANC ≥500/microliter and platelet count ≥25 x 10^3/microliter. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Dose reduction for low-dose cytarabine was not implemented in the clinical trial.

Baseline demographic and disease characteristics were similar between the venetoclax + low-dose cytarabine and placebo + low-dose cytarabine arms. The median age was 76 years (range: 36 to 93 years); 55% were male, and 71% were white, and ECOG performance status at baseline was 0 or 1 for 51% of patients and 2 for 42% of patients. There were 62% of patients with *de novo* AML and 38% with secondary AML. At baseline, 27% of patients had bone marrow blast count ≥30% – <50%, and 44% had ≥ 50%. Intermediate or poor cytogenetic risk was present in 63% and 32% patients, respectively. The following mutations were detected among 164 patients with samples: 19% (31) with *TP53*, 20% (33) with *IDH1* or *IDH2*, 18% (29) with *FLT3* and 15% (25) with *NPM1*.

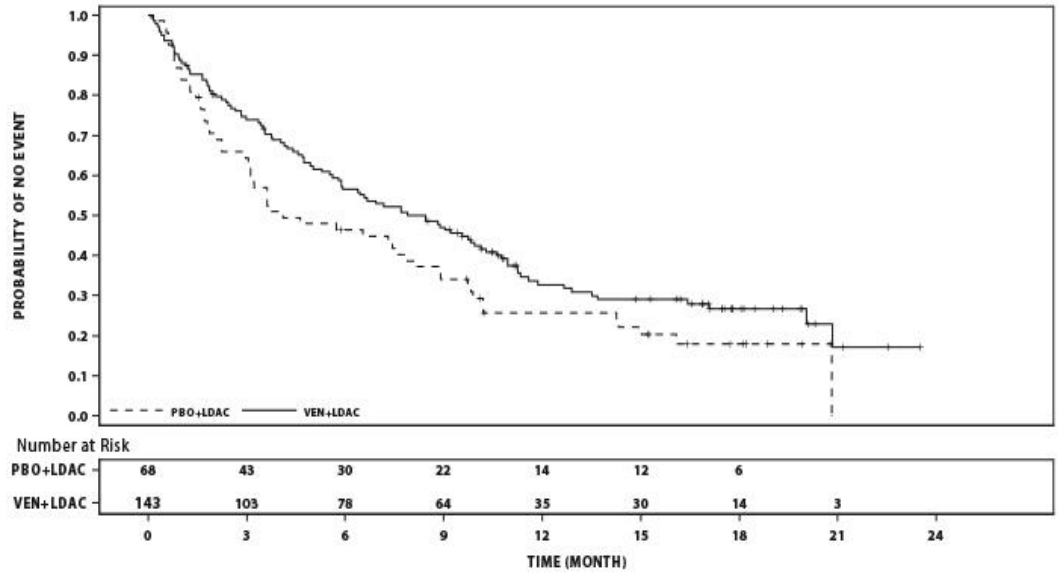
At the time of the primary analysis for OS, patients had a median follow-up of 12 months (range: 0.1 to 17.6 months). The median OS in the venetoclax + low-dose cytarabine arm was 7.2 months (95% CI: 5.6, 10.1) and in the placebo with low-dose cytarabine arm was 4.1 months (95% CI: 3.1, 8.8). The hazard ratio was 0.75 (95% CI: 0.52, 1.07; p=0.114) representing a 25% reduction in the risk of death for patients treated with venetoclax + low-dose cytarabine. The Kaplan-Meier curve for OS is shown in Figure 7.

Figure 7: Kaplan-Meier Curves of Overall Survival (Primary Analysis) in VIALE-C



At the time of an additional analysis for OS, patients had a median follow-up of 17.5 months (range: 0.1 to 23.5 months). The median OS in the venetoclax + low-dose cytarabine arm was 8.4 months (95% CI: 5.9, 10.1) and in the placebo + low-dose cytarabine arm was 4.1 months (95% CI: 3.1, 8.1). The hazard ratio was 0.70 (95% CI: 0.50, 0.99, nominal p = 0.040) representing a 30% reduction in the risk of death for patients treated with venetoclax + low-dose cytarabine. The Kaplan-Meier curve for OS with 6 additional months of follow up is shown in Figure 8.

Figure 8: Kaplan-Meier Curves of Overall Survival (6-month Follow up Analysis) in VIALE-C



Efficacy results for secondary endpoints from the primary analysis are shown in Table 31.

Table 31. Efficacy Results for Secondary Endpoints from the Primary Analysis of VIALE-C

Endpoint	VENCLEXTA + Low-Dose Cytarabine (N = 143)	Placebo + Low-Dose Cytarabine (N = 68)
CR, n (%) (95% CI) Median DOR[a] (months) (95% CI)	39 (27) (20, 35) 11.1 (5.9, NE)	5 (7) (2, 16) 8.3 (3.1, 8.3)
CR+CRi, n (%) (95% CI) Median DOR[a] (months) (95% CI)	68 (48) (39, 56) 10.8 (5.9, NE)	9 (13) (6, 24) 6.2 (1.1, NE)
CR+CRh, n (%) (95% CI) Median DOR[a] (months) (95% CI)	67 (47) (39, 55) 11.1 (5.5, NE)	10 (15) (7, 25) 6.2 (1.1, NE)
Transfusion independence rate[b] Platelet, n (%) (95% CI) Red blood cell, n (%) (95% CI)	 68 (48) (39, 56) 58 (41) (32, 49)	 22 (32) (22, 45) 12 (18) (10, 29)

CI = confidence interval; CR+CRi = complete remission + complete remission with incomplete blood count recovery; CR+CRh = complete remission + complete remission with partial haematological recovery; DOR = duration of response; NE = Not Estimable.

[a]DOR (duration of response) was defined as time from first response of CR for DOR of CR, or from first response of CR or CRi for DOR of CR+CRi, or from first response of CR or CRh for DOR of CR+CRh, to the first date of confirmed morphologic relapse, or death due to disease progression, whichever occurred earlier. Median DOR from Kaplan-Meier estimate.

[b]Transfusion independence was defined as a period of at least 56 consecutive days (≥56 days) with no transfusion after the first dose of study drug and on or before the last dose of the study drug + 30 days or before relapse or disease progression or before the initiation of post-treatment therapy whichever is earlier.

The CR+CRi rate by initiation of Cycle 2 for venetoclax + low-dose cytarabine was 34% (95% CI: 27, 43) and for placebo + low-dose cytarabine was 3% (95% CI: 0.4, 10). The median time to first response of CR+CRi was 1.1 months (range: 0.8 to 4.7 months) with venetoclax + low-dose cytarabine treatment. The median time to best response of CR+CRi was 1.2 months (range: 0.8 to 5.9 months).

Minimal residual disease response was defined as less than one AML cell per 10^3 leukocytes in the bone marrow. For the patients who had MRD assessment (113 patients in venetoclax + low-dose cytarabine arm and 44 in placebo + low-dose cytarabine arm), the median MRD value (%) was lower in the venetoclax arm when compared to the placebo arm (0.42 and 7.45, respectively). A higher number of patients had achieved CR+CRi and MRD response on venetoclax arm compared to placebo arm: 8 patients (6%) (95% CI: 2, 11) vs 1 patient (1%) (95% CI: 0, 8), respectively.

Patient-reported fatigue was assessed by the Patient Reported Outcomes Measurement Information System (PROMIS), Cancer Fatigue Short Form (SF 7a) and health-related quality of life (HRQoL) was assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC QLQ-C30) global health status/quality of life (GHS/QoL). Patients receiving venetoclax + low-dose cytarabine did not experience meaningful decrement in fatigue or HRQoL than placebo +low-dose cytarabine, and observed reduction in PROMIS Cancer Fatigue and improvement in QHS/QoL. Relative to placebo + low-dose cytarabine, patients receiving venetoclax + low-dose cytarabine observed reduction in PROMIS Cancer Fatigue that achieved a minimum important difference (MID) between two arms of 3 points by Day 1 of Cycles 3 and 5 (-2.940 vs 1.567, -5.259 versus -0.336, respectively, with lower score indicating improvement in fatigue symptom). Patients receiving venetoclax + low-dose cytarabine observed improvement in GHS/QoL that achieved MID of

5 points on Day 1 of Cycles 5, 7 and 9 vs placebo + low-dose cytarabine (16.015 vs 2.627, 10.599 vs 3.481, and 13.299 vs 6.918, respectively, with higher score indicating improvement in quality of life). The median event-free survival for venetoclax + low-dose cytarabine was 4.7 months (95% CI, 3.7, 6.4) compared to 2.0 months (95% CI, 1.6, 3.1) for placebo + low-dose cytarabine with HR (95% CI) of 0.58 (0.42, 0.82).

M14-387

The efficacy of VENCLEXTA was established in a non-randomised clinical trial of VENCLEXTA in combination with low-dose cytarabine (N=82) in newly diagnosed patients with AML who were ineligible for intensive chemotherapy, including patients with previous exposure to a hypomethylating agent for an antecedent haematological disorder.

Patients initiated VENCLEXTA via a daily dose titration schedule to a final 600 mg once daily dose. During the dose titration schedule, patients received TLS prophylaxis and were hospitalised for monitoring. Cytarabine at a dose of 20 mg/m^2 was administered subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1. Once bone marrow assessment confirmed a remission, defined as less than 5% leukaemia blasts with cytopenia following Cycle 1 treatment, VENCLEXTA was interrupted up to 14 days or until ANC ≥500/microliter and platelet count ≥50 x 10^3/microliter. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Dose reduction for low-dose cytarabine was not implemented in the clinical trials. Table 32 summarises the baseline demographic and disease characteristics of the study population.

Table 32. Baseline Patient Characteristics for Patients with AML Treated with VENCLEXTA in Combination with Low-Dose Cytarabine in M14-387

Characteristic	VENCLEXTA in Combination with Low-Dose Cytarabine (N = 82)
Age, years; median (range)	74 (63-90)
White; %	95
Male; %	65
ECOG performance status; % 0-1 2 3	 71 28 1
Bone marrow blast; % <30% ≥30% - <50% ≥50%	 33 22 44
History of antecedent haematological disorder; %	48
Mutation Analyses; % (identified/tested)	
TP53	14 (10/70)
IDH1 or *IDH2*	26 (18/70)
FLT3	21 (15/70)
NPM1	13 (9/70)
Cytogenetic risk [a]; %	
Intermediate	60
Poor	32
No mitoses	9
[a]As defined by the National Comprehensive Cancer Network (NCCN) risk categorisation v2014	

The median follow-up was 41.7 months (range: 0.3 to 54.0 months). Efficacy results are shown in Tables 33 and 34.

Table 33. Efficacy Results for Newly Diagnosed Patients with AML Treated with VENCLEXTA in Combination with Low-Dose Cytarabine (M14-387)

Endpoint	VENCLEXTA in Combination with Low-Dose Cytarabine (N = 82)
CR, n (%) (95% CI) Median DOR[a] (months) (95% CI)	21 (26) (17 - 36) 14.8 (7.2, NR)
CRi, n (%) (95% CI) Median DOR[a] (months) (95% CI)	23 (28) (19, 39) 4.7 (2.6, 5.6)
CR+CRi, n (%) (95% CI) Median DOR (months) (95% CI)	44 (54) (42, 65) 9.8 (5.3, 14.9)
CRh, n (%) (95% CI) Median DOR[a] (months) (95% CI)	17 (21) (13, 31) 6.6 (2.8, 11.0)
CR+CRh, n (%) (95% CI) Median DOR[a] (months) (95% CI)	38 (46) (35, 58) 11.0 (6.1,28.2)
Transfusion independence rate, n/N (%) Red blood cell[b] Platelet[c]	 24/53 (45) 14/23 (61)

CI = confidence interval; NR = not reached.
CR (complete remission) was defined as absolute neutrophil count ≥1,000/microliter, platelets ≥100,000/microliter, red blood cell transfusion independence, and bone marrow with <5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
CRh (complete remission with partial haematological recovery) was defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter).
CRi (complete remission with incomplete blood count recovery) was defined as same as all of the criteria for CR except for residual neutropenia <1,000/microliter or thrombocytopenia <100,000/microliter.
[a]DOR (duration of response) was defined as time from first response of CR for DOR of CR, or from first response of CRi for DOR of CRi, or from first response of CR or CRi for DOR of CR+CRi, or from first response of CRh for DOR of CRh, or from first response of CR or CRh for DOR of CR+CRh, to the first date of relapse, clinical disease progression, or death due to disease progression, whichever occurred earlier. Median DOR from Kaplan-Meier estimate.
[b]Evaluated for patients who were dependent at baseline for red blood cell transfusion.
[c]Evaluated for patients who were dependent at baseline for platelet transfusion.

Table 34. Time to Response in Patients with AML Treated with VENCLEXTA in Combination with Low-Dose Cytarabine (M14-387)

Endpoint	VENCLEXTA in Combination with Low-Dose Cytarabine (N = 82)
Median time to BEST response of CR (months) Range (months)	3.0 (0.9 – 22.4)
Median time to FIRST response of CR+CRh (months) Range (months)	1.0 (0.8 – 9.4)
Median time to FIRST response of CR+CRi (months) Range (months)	1.4 (0.8 – 14.9)

Median overall survival for patients on VENCLEXTA in combination with low-dose cytarabine was 9.7 months (95% CI: 5.7, 14.0).

Remissions (CR or CRh) were observed across subgroups with different baseline characteristics. For patients with poor or intermediate risk cytogenetics similar remission rates were observed, the rates were 35% or 57%, respectively. For patients with the following identified mutations, the remissions were as follows: *TP53*: 20% (2/10), *IDH1/2*: 67% (12/18), *FLT3*: 33% (5/15) and *NPM1*: 89% (8/9).

Remissions (CR or CRi) were observed across subgroups with different baseline characteristics. For patients with poor or intermediate risk cytogenetics similar remissions rates were observed, the rates were 42% or 63%, respectively. For patients with the following identified mutations, the remissions were as follows: *TP53*: 30% (3/10), *IDH1/2*: 72% (13/18), *FLT3*: 40% (6/15) and *NPM1*: 89% (8/9).

Minimal residual disease was evaluated in bone marrow for patients who achieved CR or CRh following treatment with VENCLEXTA in combination with low-dose cytarabine. Of those patients, 34% (13/38) achieved MRD less than one AML cell per 10^3 leukocytes in the bone marrow.

Minimal residual disease was evaluated in bone marrow for patients who achieved CR or CRi following treatment with VENCLEXTA in combination with low-dose cytarabine. Of those patients, 32% (14/44) achieved MRD less than one AML cell per 10^3 leukocytes in the bone marrow.

Of patients treated with VENCLEXTA in combination with low-dose cytarabine, 1% (1/82) achieved a CR/CRi and subsequently received stem cell transplant.

Elderly Patients

Of the 194 patients with previously treated CLL who received venetoclax in combination with rituximab 50% were 65 years or older.

Of the 164 previously treated patients with CLL or SLL evaluated for efficacy by an IRC in Studies M13-982 and M12-175, 91 (55.5%) patients were ≥65 years of age and 28 (17.1%) patients were ≥75 years of age.

Of the 240 patients with CLL evaluated for safety from 3 open-label clinical trials, 138 (57.5%) patients were ≥65 years of age and 40 (16.7%) patients were ≥75 years of age.

There were no overall differences in safety or efficacy observed between older and younger patients in combination and monotherapy studies (see section 4.2 – **Elderly Patients**).

5.2 Pharmacokinetic properties

Absorption

Following multiple oral administrations, the maximum plasma concentration of venetoclax was reached 5 to 8 hours after dosing. Venetoclax steady state AUC increased proportionally over the dose range of 150-800 mg.

Under low-fat meal conditions, venetoclax mean (± standard deviation) steady state C_{max} was 2.1 ± 1.1 μg/mL and AUC_{24} was 32.8 ± 16.9 μg•h/mL at the 400 mg once daily dose.

Administration with a low-fat meal increased venetoclax exposure by approximately 3.4-fold and administration with a high-fat meal increased venetoclax exposure by 5.1- to 5.3-fold compared to fasting conditions. Venetoclax should be administered with a meal (see section 4.2).

Distribution

Venetoclax is highly bound to human plasma protein with the unbound fraction in plasma <0.01 across a concentration range of 1-30 micromoles (0.87-26 micrograms/mL). The mean blood-to-plasma ratio is 0.57.

The population estimate for apparent volume of distribution (Vd_{ss}/F) of venetoclax ranges from 256-321 L in patients.

Metabolism

In vitro studies demonstrated that venetoclax is predominantly metabolised by CYP3A4.

M27 was identified as a major metabolite in plasma with an inhibitory activity against BCL-2 that is at least 58-fold lower than venetoclax *in vitro*.

In vitro Studies

In vitro studies indicated that venetoclax is not an inhibitor of CYP1A2, CYP2B6, CYP2C19, CYP2D6 or CYP3A4 and not an inducer of CYP1A2, 2B6 or 3A4 at clinically relevant concentrations. Venetoclax is a weak inhibitor of UGT1A1, CYP2C8 and CYP2C9 *in vitro*, but it is not predicted to cause clinically relevant inhibition of these enzymes due to high plasma protein binding. Venetoclax is not an inhibitor of UGT1A4, UGT1A6, UGT1A9 and UGT2B7.

Venetoclax is a P-gp and BCRP substrate as well as a P-gp and BCRP inhibitor and weak OATP1B1 inhibitor *in vitro*.. Venetoclax is not expected to inhibit OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 or MATE2K at clinically relevant concentrations.

Elimination

The population estimate for the terminal elimination half-life of venetoclax is approximately 26 hours.

After a single oral administration of 200 mg radiolabeled [^{14}C]-venetoclax to healthy subjects, >99.9% of the dose was recovered in faeces and <0.1% of the dose was excreted in urine within 9 days. Unchanged venetoclax accounted for 20.8% of the administered radioactive dose excreted in faeces.

The pharmacokinetics of venetoclax does not change over time.

Pharmacokinetics in special populations

Patients with renal impairment

Based on a population pharmacokinetic analysis that included 321 subjects with mild renal impairment (CrCl ≥60 and <90 mL/min), 219 subjects with moderate renal impairment (CrCl ≥30 and <60 mL/min), 6 subjects with severe renal impairment (CrCl ≥15 and <30 mL/min) and 224 subjects with normal renal function (CrCl ≥90 mL/min), venetoclax exposures in subjects with mild, moderate or severe renal impairment are similar to those with normal renal function. The pharmacokinetics of venetoclax has not been studied in subjects with CrCl <15 mL/min or subjects on dialysis (see section 4.2 – **Renal Impairment**).

Patients with hepatic impairment

Based on a population pharmacokinetic analysis that included 69 subjects with mild hepatic impairment, 7 subjects with moderate hepatic impairment and 429 subjects with normal hepatic function, venetoclax exposures are similar in subjects with mild and moderate hepatic impairment and normal hepatic function. The National Cancer Institute (NCI) Organ Dysfunction Working Group criteria for hepatic impairment were used in the analysis. Mild hepatic impairment was defined as normal total bilirubin and aspartate transaminase (AST) > upper limit of normal (ULN) or total bilirubin >1.0 to 1.5 times

ULN, moderate hepatic impairment as total bilirubin >1.5 to 3.0 times ULN, and severe hepatic impairment as total bilirubin >3.0 ULN.

In a dedicated hepatic impairment study, venetoclax C_{max} and AUC in subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment were similar to subjects with normal hepatic function. In subjects with severe (Child-Pugh C) hepatic impairment, the mean venetoclax C_{max} was similar to subjects with normal hepatic function but venetoclax AUC was 2.3- to 2.7-fold higher than subjects with normal hepatic function (see section 4.2 – **Patients with Hepatic Impairment**).

Race/ethnicity
Based on population pharmacokinetic analyses, race does not have an effect on venetoclax clearance.

Gender/weight
Based on population pharmacokinetic analyses, sex and weight do not have an effect on venetoclax clearance.

Elderly patients
Based on population pharmacokinetic analyses, age does not have an effect on venetoclax clearance.

Paediatric patients
The pharmacokinetics of VENCLEXTA has not been evaluated in patients <18 years of age (see section 4.2).

5.3 Preclinical safety data

Animal Pharmacology and/or Toxicology
In addition to testicular germ cell loss, other toxicities observed in animal studies with venetoclax included dose-dependent reductions in lymphocytes and red blood cell mass. After cessation of dosing with venetoclax, red blood cell effects were reversible, whereas partial reversibility of lymphocytes was observed at the end of an 18-week recovery period. Both B- and T- cells were affected, but the most significant decreases occurred with B-cells. The M27 metabolite orally administered to mice had effects similar to venetoclax (decreased lymphocytes and red blood cell mass) but of lesser magnitude, consistent with its low *in vitro* pharmacologic potency.

Venetoclax also caused single-cell necrosis in various tissues, including the gallbladder and exocrine pancreas, with no evidence of disruption of tissue integrity or organ dysfunction; these findings were minimal to mild in magnitude. Following a 4-week dosing period and subsequent 4-week recovery period, minimal single-cell necrosis was still present in some tissues and reversibility has not been assessed following longer periods of dosing or recovery.

After approximately 3 months of daily dosing in dogs, venetoclax caused progressive white discoloration of the hair coat, due to loss of melanin pigment in the hair. No changes in the quality of the hair coat or skin were observed, nor in other pigmented tissues examined (e.g., the iris and the ocular fundus of the eye). Reversibility of the hair coat changes has not been assessed in dogs.

In pregnant rats, maternal systemic exposures (AUC) to venetoclax were approximately 14-times higher than the exposure in humans at a 400 mg dose. Measurable levels of radioactivity in foetal tissues (liver, GI tract) were >15-fold lower than maternal levels in the same tissues. Venetoclax derived radioactivity was not detected in foetal blood, brain, eye, heart, kidney, lung, muscle or spinal cord.

Venetoclax was administered (single dose; 150 mg/kg oral) to lactating rats 8-10 days parturition. Venetoclax in milk was 1.6 times lower than in plasma. Parent drug (venetoclax) represented the majority of the total drug-related material in milk, with trace levels of three metabolites.

Genotoxicity

Venetoclax was not mutagenic in an *in vitro* bacterial mutagenicity (Ames) assay, did not induce numerical or structural aberrations in an *in vitro* chromosome aberration assay using human peripheral blood lymphocytes, and was not clastogenic in an *in vivo* mouse bone marrow micronucleus assay at a single oral dose up to 835 mg/kg. The M27 metabolite was negative for genotoxic activity in *in vitro* Ames and chromosome aberration assays.

Carcinogenicity

Venetoclax and the M27 major human metabolite were not carcinogenic in a 6-month transgenic (Tg.rasH2) mouse carcinogenicity study at oral doses up to 400 mg/kg/day of venetoclax, and at a single dose level of 250 mg/kg/day of M27. Exposure margins (AUC), relative to the clinical AUC at 400 mg/day, were approximately 2-fold for venetoclax and 5.8-fold for M27.

Paediatric Population

In a juvenile toxicology study, mice were administered venetoclax at 10, 30, or 100 mg/kg/day by oral gavage from 7 to 60 days of age. Clinical signs of toxicity included decreased activity, dehydration, skin pallor, and hunched posture at $\geqslant$30 mg/kg/day. In addition, mortality and body weight effects occurred at 100 mg/kg/day. Other venetoclax-related effects were reversible decreases in lymphocytes at $\geqslant$10 mg/kg/day, which were consistent with adult mice, and considered non-adverse.

The venetoclax No Observed Adverse Effect Level (NOAEL) of 10 mg/kg/day in mice is approximately 0.06 times a clinical dose of 400 mg on a mg/m^2 basis for a 20 kg child.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

VENCLEXTA 10 mg film-coated tablets contain the following inactive ingredients: copovidone, colloidal anhydrous silica, polysorbate 80, sodium stearylfumarate, calcium hydrogen phosphate, iron oxide yellow, polyvinyl alcohol, macrogol 3350, purified talc, and titanium dioxide.

VENCLEXTA 50 mg film-coated tablets contain the following inactive ingredients: copovidone, colloidal anhydrous silica, polysorbate 80, sodium stearylfumarate, calcium hydrogen phosphate, iron oxide yellow, iron oxide red, iron oxide black, polyvinyl alcohol, purified talc, macrogol 3350 and titanium dioxide.

VENCLEXTA 100 mg film-coated tablets contain the following inactive ingredients: copovidone, colloidal anhydrous silica, polysorbate 80, sodium stearylfumarate, calcium hydrogen phosphate, iron oxide yellow, polyvinyl alcohol, macrogol 3350, purified talc, and titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

VENCLEXTA 10 mg and 50 mg tablets: 24 months
VENCLEXTA 100 mg tablets: 36 months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

VENCLEXTA is dispensed as follows:

Packaging Presentation	Number of Tablets
Starting Pack for CLL/SLL	Each Starting Pack contains four weekly wallets: • Week 1 (14 x 10 mg tablets) • Week 2 (7 x 50 mg tablets) • Week 3 (7 x 100 mg tablets) • Week 4 (14 x 100 mg tablets) Each wallet contains one blister pack
10 mg Wallet	14 x 10 mg tablets
50 mg Wallet	7 x 50 mg tablets
100 mg Blister pack	7, 14, 112 x 100 mg tablets
100 mg Bottle	120 x 100 mg tablets 180 x 100 mg tablets

Not all presentations may be marketed.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

AbbVie Limited
6th Floor, 156-158 Victoria St
Wellington, 6011
New Zealand

Phone: 0800 900 030

9. DATE OF FIRST APPROVAL

2 November 2017

10. DATE OF REVISION OF THE TEXT

20 August 2020
Version 12

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Study GO28667 replaced with MURANO. Study BO25323 replaced with CLL14.
4.1	Updated to include new indication for AML.
4.2	Starting pack clarification added to the CLL/SLL dose titration phase table. Obinutuzumab dosing clarified in first line CLL/SLL dosing schedule. Added dosage instructions for combination therapy in AML treatment. Updated guidance for TLS prophylaxis and laboratory monitoring in CLL. AML TLS prophylaxis measures added. AML dose modifications based on toxicities recommendations added. Dose modifications for use with CYP3A inhibitors section amended due to different dose modifications for the AML indication. Renal impairment information updated.
4.4	Updated guidance for TLS. Neutropenia precaution updated with AML information and deletion of unrequired references. Renal impairment information relocated to sections 4.2 and 5.2.
4.5	Posaconazole drug interaction updated.
4.6	Results in fertility section amended to 1 decimal point. Pregnancy section updated to include M27 metabolite information from animal data. Breastfeeding section updated to refer to newly added animal data in Section 5.3.
4.8	CLL/SLL monotherapy information updated with safety changes in line with the CCDS. AML information included. Study numbers included in TLS - CLL/SLL monotherapy section.
5.1	Updated results for CLL/SLL studies: CLL14, Study M12-175, Study M14-032. Added results for AML studies: VIALE-A, M14-358, VIALE-C, M14-387.
5.2	Duplicate text removed from *in vitro* studies section. Renal impairment pharmacokinetics information updated.
5.3	M27 metabolite information relocated to animal pharmacology and/or toxicology section. Pregnancy and lactation animal information added. Carcinogenicity data updated.