# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Venclyxto 100 mg film-coated tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg of venetoclax.
For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).
Pale yellow, oblong biconvex shaped tablet 17.2 mm long, 9.5 mm wide debossed with V on one side and 100 on the other.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Venclyxto is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL):

- in combination with acalabrutinib with or without obinutuzumab
- in combination with obinutuzumab (see section 5.1)
- in combination with ibrutinib

Venclyxto in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.

Venclyxto monotherapy is indicated for the treatment of CLL:

- in the presence of 17p deletion or *TP53* mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or
- in the absence of 17p deletion or *TP53* mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.

Venclyxto in combination with a hypomethylating agent or low-dose cytarabine is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.

## 4.2 Posology and method of administration

Treatment with venetoclax should be initiated and supervised by a physician experienced in the use of anticancer medicinal products. Patients treated with venetoclax may develop tumour lysis syndrome (TLS). Information described in this section, including risk assessment, prophylactic measures, dose-titration schedule, laboratory monitoring, and drug interactions should be followed to prevent and reduce the risk of TLS.

Posology

*Chronic lymphocytic leukaemia*

*Dose-titration schedule*

The starting dose is 20 mg of venetoclax once daily for 7 days. The dose must be gradually increased over a period of 5 weeks up to the daily dose of 400 mg as shown in Table 1.

Table 1: Dose increase schedule in patients with CLL

| Week | Venetoclax daily dose |
|---|---|
| 1 | 20 mg |
| 2 | 50 mg |
| 3 | 100 mg |
| 4 | 200 mg |
| 5 | 400 mg |

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

*Venetoclax in combination with acalabrutinib with or without obinutuzumab*

Administer acalabrutinib 100 mg orally on Cycle 1 Day 1 approximately every 12 hours for a total of 14 cycles of treatment. Each cycle is 28 days.

Start the 5-week venetoclax dose-titration schedule (Table 1) on Cycle 3 Day 1. After completing the dose-titration schedule, the recommended dose of venetoclax is 400 mg once daily until the last day of Cycle 14.

If venetoclax is given in combination with acalabrutinib and obinutuzumab, administer obinutuzumab 100 mg on Cycle 2 Day 1, followed by 900 mg, which may be administered on Day 1 or Day 2. Administer 1000 mg on Days 8 and 15 of Cycle 2 and on Day 1 of Cycles 3 to 7. Obinutuzumab is administered for a total of 6 cycles.

*Venetoclax in combination with obinutuzumab*

Venetoclax is given for a total of 12 cycles, each cycle consisting of 28 days: 6 cycles in combination with obinutuzumab, followed by 6 cycles of venetoclax as a single agent.

Administer obinutuzumab 100 mg on Cycle 1 Day 1, followed by 900 mg which may be administered on Day 1 or Day 2. Administer 1000 mg on Days 8 and 15 of Cycle 1 and on Day 1 of each subsequent 28-day cycle, for a total of 6 cycles.

Start the 5-week venetoclax dose-titration schedule (see Table 1) on Cycle 1 Day 22 and continue through Cycle 2 Day 28.

After completing the dose-titration schedule, the recommended dose of venetoclax is 400 mg once daily from Cycle 3 Day 1 of obinutuzumab to the last day of Cycle 12.

*Venetoclax in combination with ibrutinib*
Start ibrutinib (420 mg once daily) as a single agent for 3 cycles (1 cycle is 28 days), followed by 12 cycles of venetoclax in combination with ibrutinib. Beginning on Cycle 4 Day 1, administer venetoclax according to the dose increase schedule (see Table 1). After completing the dose increase schedule, patients should continue venetoclax 400 mg once daily in combination with ibrutinib 420 mg orally once daily to the end of Cycle 15.
Refer to the ibrutinib prescribing information for additional information.

*Post-titration dose for venetoclax in combination with rituximab*
The recommended dose of venetoclax in combination with rituximab is 400 mg once daily (see section 5.1 for details of the combination regimen).

Administer rituximab after the patient has completed the dose-titration schedule and has received the recommended daily dose of 400 mg venetoclax for 7 days.

Venetoclax is taken for 24 months from Cycle 1 Day 1 of rituximab (see section 5.1).

*Post-titration dose for venetoclax monotherapy*
The recommended dose of venetoclax is 400 mg once daily. Treatment is continued until disease progression or no longer tolerated by the patient.

*Acute myeloid leukaemia*
The dose of venetoclax depends upon the combination agent.
The recommended venetoclax dosing schedule (including dose-titration) is shown in Table 2.

Table 2: Dose increase schedule in patients with AML

| Day | Venetoclax daily dose |
|---|---|
| 1 | 100 mg |
| 2 | 200 mg |

| | | |
|---|---|---|
| 3 | 400 mg | |
| 4 and beyond | 400 mg<br>when dosing in combination with a hypomethylating agent | 600 mg<br>when dosing in combination with low-dose cytarabine |

A hypomethylating agent (azacitidine or decitabine) or low-dose cytarabine should be initiated on Cycle 1 Day 1.

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

or

Decitabine should be administered at 20 mg/m$^2$ of BSA intravenously on Days 1-5 of each 28-day cycle beginning on Cycle 1 Day 1.

or

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.

Refer to the azacitidine or decitabine or low-dose cytarabine prescribing information for additional information.

Venetoclax dosing may be interrupted as needed for management of adverse reactions and blood count recovery (see Table 6).

Venetoclax, in combination with a hypomethylating agent (azacitidine or decitabine) or low-dose cytarabine, should be continued until disease progression or unacceptable toxicity is observed.

*Prevention of tumour lysis syndrome (TLS)*
Patients treated with venetoclax may develop TLS. The appropriate section below should be referred to for specific details on management by disease indication.

Chronic lymphocytic leukaemia
Venetoclax can cause rapid reduction in tumour, and thus poses a risk for TLS in the initial 5-week dose-titration phase in all patients with CLL, regardless of tumour burden and other patient characteristics. Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax and at each dose increase. Patient-specific factors for level of TLS risk should be assessed and prophylactic hydration and anti-hyperuricaemics should be provided to patients prior to first dose of venetoclax to reduce risk of TLS.

The risk of TLS is a continuum based on multiple factors, including comorbidities, particularly 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 venetoclax treatment (see section 4.4).

Prior to initiating venetoclax, tumour burden assessment, including radiographic evaluation (e.g., CT scan), must be performed for all patients. Blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) should be assessed and pre-existing abnormalities corrected.
Table 3 below describes the recommended TLS prophylaxis and monitoring during venetoclax treatment based on tumour burden determination from clinical study data (see section 4.4). In addition, all patient comorbidities should be considered for risk-appropriate prophylaxis and monitoring, either outpatient or in hospital.

Table 3. Recommended TLS prophylaxis based on tumour burden in patients with CLL

| **Tumour burden** | | **Prophylaxis** | | **Blood chemistry monitoring[c,d]** |
|---|---|---|---|---|
| | | | | |
| | | Hydration[a] | Anti-hyperuricaemics[b] | Setting and frequency of assessments |
| Low | All LN <5 cm<br>AND<br>ALC<br><25 x$10^9$/L | Oral<br>(1.5-2 L) | Allopurinol | Outpatient<br>• For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours<br>• For subsequent dose increases: Pre-dose |
| Medium | Any LN 5 cm to <10 cm<br>OR<br>ALC<br>≥25 x$10^9$/L | Oral<br>(1.5-2 L)<br>and consider additional intravenous | Allopurinol | Outpatient<br>• For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours<br>• For subsequent dose increases: Pre-dose<br>• 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<br>OR<br>ALC<br>≥25 x$10^9$/L<br>AND<br>any LN ≥5 cm | Oral (1.5-2 L) and intravenous (150-200 ml/hr as tolerated) | Allopurinol; consider rasburicase if baseline uric acid is elevated | In hospital<br>• For first dose of 20 mg and 50 mg: Pre-dose, 4, 8, 12 and 24 hours<br>Outpatient<br>• For subsequent dose increases: Pre-dose, 6 to 8 hours, 24 hours |
| ALC = absolute lymphocyte count; CrCl = creatinine clearance; LN = lymph node.<br>[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.<br>[b]Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of venetoclax.<br>[c]Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.<br>[d]At subsequent dose increases, monitor blood chemistries at 6 to 8 hours and at 24 hours for patients who continue to be at risk of TLS. | | | | |

*Dose modifications for tumour lysis syndrome and other toxicities*
Chronic lymphocytic leukaemia

Dosing interruption and/or dose reduction for toxicities may be required. See Table 4 and Table 5 for recommended dose modifications for toxicities related to venetoclax.

Table 4. Recommended venetoclax dose modifications for toxicities[a] in CLL

| 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 to 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 5). |
| | | For any events of clinical TLS,[b] resume at a reduced dose following resolution (see Table 5). |
| Non-haematologic toxicities | | |
| Grade 3 or 4 non-haematologic toxicities | 1st occurrence | Interrupt venetoclax.<br>Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose. No dose modification is |

| | | |
|---|---|---|
| | | required. |
| | 2nd and subsequent occurrences | Interrupt venetoclax.<br>Follow dose reduction guidelines in Table 5 when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the physician. |
| Haematologic toxicities | | |
| Grade 3 neutropenia with infection or fever; or Grade 4 haematologic toxicities (except lymphopenia) | 1st occurrence | Interrupt venetoclax.<br>To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with venetoclax if clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose. |
| | 2nd and subsequent occurrences | Interrupt venetoclax.<br>Consider using G-CSF as clinically indicated.<br>Follow dose reduction guidelines in Table 5 when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the physician. |
| Consider discontinuing venetoclax for patients who require dose reductions to less than 100 mg for more than 2 weeks.<br>[a]Adverse reactions were graded using NCI CTCAE version 4.0.<br>[b]Clinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or seizures and/or sudden death (see section 4.8). | | |

Table 5: Dose modification for TLS and other toxicities for patients with CLL

| **Dose at interruption (mg)** | **Restart dose (mg[a])** |
|---|---|
| 400 | 300 |
| 300 | 200 |
| 200 | 100 |
| 100 | 50 |
| 50 | 20 |
| 20 | 10 |
| [a]The modified dose should be continued for 1 week before increasing the dose. | |

For patients who have had a dosing interruption lasting more than 1 week during the first 5 weeks of dose-titration or more than 2 weeks after completing the dose-titration phase, TLS risk should be reassessed to determine if restarting at a reduced dose is necessary (e.g., all or some levels of the dose-titration; see Table 5).

Acute myeloid leukaemia

The venetoclax daily dose-titration is 3 days with azacitidine or decitabine or 4 days with low-dose cytarabine (see Table 2).

Prophylaxis measures listed below should be followed:
All patients should have white blood cell count $<25 \times 10^9$/l prior to initiation of venetoclax and cytoreduction prior to treatment may be required.

All patients should be adequately hydrated and receive anti-hyperuricaemic agents prior to initiation of first dose of venetoclax and during dose-titration phase.

Assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) and correct pre-existing abnormalities prior to initiation of treatment with venetoclax.

Monitor blood chemistries for TLS at pre-dose, 6 to 8 hours after each new dose during titration and 24 hours after reaching 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 reducing venetoclax starting dose.

Monitor blood counts frequently through resolution of cytopenias. Dose modification and interruptions for cytopenias are dependent on remission status. Dose modifications of venetoclax for adverse reactions are provided in Table 6.

Table 6: Recommended dose modifications for adverse reactions in AML

| **Adverse Reaction** | **Occurrence** | **Dosage Modification** |
|---|---|---|
| **Haematologic Adverse Reactions** | | |
| Grade 4 neutropenia (ANC < 500/microlitre) with or without fever or infection; or grade 4 thrombocytopenia (platelet count $<25 \times 10^3$/microlitre) | Occurrence prior to achieving remission[a] | In most instances, do not interrupt venetoclax in combination with azacitidine or decitabine or low dose cytarabine due to cytopenias prior to achieving remission. |
| | First occurrence after achieving remission and lasting at least 7 days | Delay subsequent cycle of venetoclax in combination with azacitidine or decitabine or low dose cytarabine and monitor blood counts. Administer granulocyte-colony stimulating factor (G-CSF) if clinically indicated for neutropenia. Upon resolution to grade 1 or 2, resume venetoclax at the same dose in combination with azacitidine or decitabine or low dose cytarabine. |
| | Subsequent occurrences in cycles after achieving remission and lasting | Delay subsequent cycle of venetoclax in combination with azacitidine or decitabine or low dose |

| Adverse Reaction | Occurrence | Dosage Modification |
|---|---|---|
| | 7 days or longer | cytarabine and monitor blood counts. Administer G-CSF if clinically indicated for neutropenia. Upon resolution to grade 1 or 2, resume venetoclax at the same dose in combination with azacitidine or decitabine or low dose cytarabine, and reduce venetoclax duration by 7 days during each of the subsequent cycles, such as 21 days instead of 28 days. Refer to the azacitidine prescribing information for additional information. |
| **Non-Hematologic Adverse Reactions** | | |
| Grade 3 or 4 non-hematologic toxicities | Any occurrence | Interrupt venetoclax if not resolved with supportive care. Upon resolution to grade 1 or baseline level, resume venetoclax at the same dose. |
| [a]Consider bone marrow evaluation. | | |

*Dose modifications for use with CYP3A inhibitors*

Concomitant use of venetoclax 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 and for other toxicities (see section 4.5).

In patients with CLL, concomitant use of venetoclax with strong CYP3A inhibitors is contraindicated at initiation and during the dose-titration phase (see sections 4.3, 4.4, and 4.5).

In all patients, if a CYP3A inhibitor must be used, follow the recommendations for managing drug-drug interactions summarized in Table 7. Patients should be monitored more closely for signs of toxicities and the dose may need to be further adjusted. The venetoclax dose that was used prior to initiating the CYP3A inhibitor should be resumed 2 to 3 days after discontinuation of the inhibitor (see sections 4.3, 4.4 and 4.5).

Table 7: Management of potential venetoclax interactions with CYP3A inhibitors

| Inhibitor | Phase | CLL | AML |
|---|---|---|---|
| **Strong CYP3A inhibitor** | Initiation and dose-titration phase | Contraindicated | Day 1 – 10 mg<br>Day 2 – 20 mg<br>Day 3 – 50 mg<br>Day 4 – 100 mg or less |
| | Steady daily dose (After dose-titration phase) | Reduce the venetoclax dose to 100 mg or less (or by at least 75% if already modified for other reasons) | |
| **Moderate CYP3A inhibitor**[a] | All | Reduce the venetoclax dose by at least 50% | |
| [a]In patients with CLL, avoid concomitant use of venetoclax with moderate CYP3A inhibitors at initiation and during the dose-titration phase. Consider alternative medicinal products or reduce the venetoclax dose as described in this table. | | | |

*Missed dose*

If a patient misses a dose of venetoclax within 8 hours of the time it is usually taken, the patient should take the missed dose as soon as possible on the same day. If a patient misses a dose by more than 8 hours, the patient should not take the missed dose and should resume the usual dosing schedule the following day.

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

*Special populations*

*Elderly*

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

*Renal impairment*

Patients with reduced renal function (CrCl <80 ml/min) may require more intensive prophylaxis and monitoring to reduce the risk of TLS at initiation and during the dose-titration phase (see "Prevention of tumour lysis syndrome (TLS)" above). Venetoclax should be administered to patients with severe renal impairment (CrCl ≥15 ml/min and <30 ml/min) or end-stage renal disease (ESRD) requiring dialysis (CrCL <15 ml/min) only if the benefit outweighs the risk and patients should be monitored closely for signs of toxicity due to increased risk of TLS (see section 4.4).

No dose adjustment is needed for patients with mild, moderate, severe renal impairment or end-stage renal disease requiring dialysis (see section 5.2).

*Hepatic impairment*

No dose adjustment is recommended in patients with mild or moderate hepatic impairment. Patients with moderate hepatic impairment should be monitored more closely for signs of toxicity at initiation and during the dose-titration phase (see section 4.8).

A dose reduction of at least 50% throughout treatment is recommended for patients with severe hepatic impairment (see section 5.2). These patients should be monitored more closely for signs of toxicity (see section 4.8).

*Paediatric population*
The safety and efficacy of venetoclax in children aged less than 18 years have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration
Venclyxto film-coated tablets are for oral use. Patients should be instructed to swallow the tablets whole with water at approximately the same time each day. The tablets should be taken with a meal in order to avoid a risk for lack of efficacy (see section 5.2). The tablets should not be chewed, crushed, or broken before swallowing.

During the dose-titration phase, venetoclax should be taken in the morning to facilitate laboratory monitoring.

Grapefruit products, Seville oranges, and starfruit (carambola) should be avoided during treatment with venetoclax (see section 4.5).

## 4.3 Contraindications

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

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

In all patients, concomitant use of preparations containing St. John's wort (see sections 4.4 and 4.5).

## 4.4 Special warnings and precautions for use

Tumour lysis syndrome

Tumour lysis syndrome, including fatal events and renal failure requiring dialysis, has occurred in patients treated with venetoclax (see section 4.8).

Venetoclax can cause rapid reduction in tumour, 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 to 8 hours following the first dose of venetoclax and at each dose increase. During post-marketing surveillance, TLS, including fatal events, has been reported after a single 20 mg dose of venetoclax. Information described in section 4.2, including risk assessment, prophylactic measures, dose-titration

and modification schedule, laboratory monitoring, and drug interactions should be followed to prevent and reduce the risk of TLS.

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

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. More intensive measures (intravenous hydration, frequent monitoring, hospitalisation) should be employed as overall risk increases. Dosing should be interrupted if needed; when restarting venetoclax, dose modification guidance should be followed (see Table 4 and Table 5). The instructions for "Prevention of tumour lysis syndrome (TLS)" should be followed (see section 4.2).

Concomitant use of this medicinal product with strong or moderate CYP3A inhibitors increases venetoclax exposure and may increase the risk for TLS at initiation and during the dose-titration phase (see sections 4.2 and 4.3). Also, inhibitors of P-gp or BCRP may increase venetoclax exposure (see section 4.5).

Neutropenia and infections

In patients with CLL, grade 3 or 4 neutropenia has been reported in patients treated with venetoclax in combination studies and in monotherapy studies (see section 4.8).

In patients with AML, grade 3 or 4 neutropenia are common before starting treatment. The neutrophil counts can worsen with venetoclax in combination with a hypomethylating agent 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 reductions are recommended for patients with severe neutropenia (see section 4.2).

Serious infections, including sepsis with fatal outcome, have been reported (see section 4.8). Monitoring of any signs and symptoms of infection is required. Suspected infections are to receive prompt treatment, including antimicrobials, dose interruption or reduction, and use of growth factors (e.g. G-CSF) as appropriate (see section 4.2).

Immunisation

The safety and efficacy of immunisation with live attenuated vaccines during or following venetoclax therapy have not been studied. Live vaccines should not be administered during treatment and thereafter until B-cell recovery.

CYP3A inducers

Co-administration of CYP3A4 inducers may lead to decreased venetoclax exposure and consequently a risk for lack of efficacy. Concomitant use of venetoclax with strong or moderate CYP3A4 inducers should be avoided (see sections 4.3 and 4.5).

Women of childbearing potential
Women of childbearing potential must use a highly effective method of contraception while taking venetoclax (see section 4.6).

Excipients with known effect
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium free".

## 4.5 Interaction with other medicinal products and other forms of interaction

Venetoclax is predominantly metabolised by CYP3A.

Agents that may alter venetoclax plasma concentrations

*CYP3A inhibitors*
Co-administration of 400 mg once daily ketoconazole, a strong CYP3A, P-gp and BCRP inhibitor, for 7 days in 11 patients increased venetoclax $C_{max}$ to 2.3-fold and AUC to 6.4-fold. Co-administration of 50 mg once daily ritonavir, a strong CYP3A and P-gp inhibitor, for 14 days in 6 healthy subjects increased venetoclax $C_{max}$ to 2.4-fold and AUC by 7.9-fold. 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 patients increased venetoclax $C_{max}$ to 1.6-fold and 1.9-fold, and AUC to 1.9-fold and 2.4-fold, respectively. Co-administration of venetoclax with other strong CYP3A4 inhibitors is predicted to increase venetoclax AUC by on average 5.8- to 7.8-fold.

For patients requiring concomitant use of venetoclax with strong CYP3A inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, ritonavir) or moderate CYP3A inhibitors (e.g., ciprofloxacin, diltiazem, erythromycin, fluconazole, verapamil), venetoclax dosing should be administered according to Table 7. Patients should be monitored more closely for signs of toxicities and the dose may need to be further adjusted. The venetoclax dose that was used prior to initiating the CYP3A inhibitor should be resumed 2 to 3 days after discontinuation of the inhibitor (see section 4.2).

Grapefruit products, Seville oranges, and starfruit (carambola) should be avoided during treatment with venetoclax as they contain inhibitors of CYP3A.

*P-gp and BCRP inhibitors*
Venetoclax is a substrate for P-gp and BCRP. Co-administration of a 600 mg single dose of rifampicin, a P-gp inhibitor, in 11 healthy subjects increased

venetoclax $C_{max}$ by 106% and AUC by 78%. Concomitant use of venetoclax with P-gp and BCRP inhibitors at initiation and during the dose-titration phase should be avoided; if a P-gp and BCRP inhibitor must be used, patients should be monitored closely for signs of toxicities (see section 4.4).

*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 venetoclax with strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampicin) or moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) should be avoided. Alternative treatments with less CYP3A induction should be considered. Preparations containing St. John's wort are contraindicated during treatment with venetoclax, as efficacy may be reduced (see section 4.3).

*Azithromycin*

In a drug-drug interaction study in 12 healthy subjects, co-administration of 500 mg of azithromycin on the first day followed by 250 mg of azithromycin once daily for 4 days decreased venetoclax $C_{max}$ by 25% and AUC by 35%. No dose adjustment is needed during short-term use of azithromycin when administered concomitantly with venetoclax.

*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.

*Bile acid sequestrants*

Co-administration of bile acid sequestrants with venetoclax is not recommended as this may reduce the absorption of venetoclax. If a bile acid sequestrant is to be co-administered with venetoclax, the SmPC for the bile acid sequestrant should be followed to reduce the risk for an interaction, and venetoclax should be administered at least 4-6 hours after the sequestrant.

Agents that may have their plasma concentrations altered by venetoclax

*Warfarin*

In a drug-drug interaction study in three healthy volunteers, administration of a single dose of 400 mg 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 normalized ratio (INR) be monitored closely in patients receiving warfarin.

*Substrates of P-gp, BCRP, and OATP1B1*

Venetoclax is a P-gp, BCRP and OATP1B1 inhibitor *in vitro*. In a drug-drug interaction study, administration of a single 100 mg dose of venetoclax with 0.5 mg digoxin, a P-gp substrate, resulted in a 35% increase in digoxin $C_{max}$ and a 9% increase in digoxin AUC. Co-administration of narrow therapeutic

index P-gp, or BCRP substrates (e.g., digoxin, dabigatran, everolimus, sirolimus) with venetoclax should be avoided.

If a narrow therapeutic index P-gp or BCRP substrate must be used, it should be used with caution. For an orally administered P-gp or BCRP substrate sensitive to inhibition in the gastrointestinal tract (e.g., dabigatran etexilate), its administration should be separated from venetoclax administration as much as possible to minimise a potential interaction.

If a statin (OATP substrate) is used concomitantly with venetoclax, close monitoring of statin-related toxicity is recommended.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Women should avoid becoming pregnant while taking Venclyxto and for at least 30 days after ending treatment. Therefore, women of childbearing potential must use highly effective contraceptive measures while taking venetoclax and for 30 days after stopping treatment. It is currently unknown whether venetoclax may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method.

Pregnancy

Based on embryo-foetal toxicity studies in animals (see section 5.3), venetoclax may harm the foetus when administered to pregnant women.

There are no adequate and well-controlled data from the use of venetoclax in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Venetoclax is not recommended during pregnancy and in women of childbearing potential not using highly effective contraception.

Breast-feeding
It is unknown whether venetoclax or its metabolites are excreted in human milk.

A risk to the breast-feeding child cannot be excluded.

Breast-feeding should be discontinued during treatment with Venclyxto.

Fertility

No human data on the effect of venetoclax on fertility are available. Based on testicular toxicity in dogs at clinically relevant exposures, male fertility may be compromised by treatment with venetoclax (see section 5.3). Before starting treatment, counselling on sperm storage may be considered in some male patients.

## 4.7 Effects on ability to drive and use machines

Venclyxto has no or negligible influence on the ability to drive and use machines. Fatigue and dizziness have been reported in some patients taking venetoclax and should be considered when assessing a patient's ability to drive or operate machines.

## 4.8 Undesirable effects

Summary of safety profile

Chronic lymphocytic leukaemia

The overall safety profile of Venclyxto is based on data from 758 patients with CLL treated in clinical studies with venetoclax in combination with obinutuzumab or rituximab or as monotherapy. The safety analysis included patients from two phase 3 studies (CLL14 and MURANO), two phase 2 studies (M13-982 and M14-032), and one phase 1 study (M12-175). CLL14 was a randomised, controlled study in which 212 patients with previously untreated CLL and comorbidities received venetoclax in combination with obinutuzumab. MURANO was a randomised, controlled study in which 194 patients with previously treated CLL received venetoclax in combination with rituximab. In the phase 2 and phase 1 studies, 352 patients with previously treated CLL, which included 212 patients with 17p deletion and 146 patients who had failed a B-cell receptor pathway inhibitor were treated with venetoclax monotherapy (see section 5.1).

The most commonly occurring adverse reactions (≥20%) of any grade in patients receiving venetoclax in the combination studies with obinutuzumab or rituximab were neutropenia, diarrhoea, and upper respiratory tract infection. In the monotherapy studies, the most common adverse reactions were neutropenia/neutrophil count decreased, diarrhoea, nausea, anaemia, fatigue, and upper respiratory tract infection.

The most frequently reported serious adverse reactions (≥2%) in patients receiving venetoclax in combination with obinutuzumab or rituximab were pneumonia, sepsis, febrile neutropenia, and TLS. In the monotherapy studies, the most frequently reported serious adverse reactions (≥2%) were pneumonia and febrile neutropenia.

AMPLIFY was a randomised, controlled study in which 575 patients with previously untreated CLL without del(17p) or *TP53* mutation received venetoclax in combination with acalabrutinib with or without obinutuzumab. For a description of adverse reactions in patients receiving venetoclax in combination with acalabrutinib with or without obinutuzumab, refer to the acalabrutinib SmPC.

*GLOW (CLL3011)*
GLOW was an open-label randomized (1:1) phase 3 study in patients with previously untreated CLL/SLL who were 65 years or older, or patients <65 years of age with a Cumulative Illness Rating Scale (CIRS) score >6 or CrCL <70 mL/min. Patients received 3 cycles of single-agent ibrutinib (420 mg/day orally). Starting at Cycle 4, venetoclax was added (starting with

the 5-week dose-titration to the recommended daily dose of 400 mg) to the ibrutinib regimen continuously for 12 additional cycles.
At the time of primary data analysis (26 February 2021), the median duration of exposure was 13.8 months in the venetoclax + ibrutinib arm and 5.13 months in the chlorambucil + obinutuzumab arm.
In the venetoclax + ibrutinib arm, adverse events led to discontinuation of venetoclax in 11% of patients, dose reductions in 17% of patients, and dose interruptions in 42% of patients. The most common adverse reaction that led to dose interruption of venetoclax was neutropenia.

*CAPTIVATE (PCYC-1142-CA)*
The safety of venetoclax in combination with ibrutinib was evaluated in a multi-center, 2-cohort study assessing both minimal residual disease (MRD)-guided discontinuation and fixed duration (FD) therapy in adult patients who were 70 years or younger with previously untreated CLL or SLL. Patients in both cohorts received 3 cycles of single-agent ibrutinib (420 mg/day orally). Starting at Cycle 4, venetoclax was added (starting with the 5-week dose titration to the recommended daily dose of 400 mg) to the ibrutinib regimen continuously for at least 12 additional cycles. Safety was assessed in an all-treated pool consisting of the MRD-guided cohort (first 16 cycles) plus the FD cohort.
At the time of primary data analysis (12 November 2020), the median duration of exposure was 11.5 months for venetoclax and 14.1 months for ibrutinib. Adverse events led to discontinuation of venetoclax in 3% of patients and dose reductions in 12% of patients.

Acute myeloid leukaemia

The overall safety profile of Venclyxto is based on data from 456 patients with newly diagnosed acute myeloid leukaemia (AML) treated in clinical studies with venetoclax in combination with a hypomethylating agent (azacitidine or decitabine) (VIALE-A phase 3 randomised, and M14-358 phase 1 non-randomised) or low dose cytarabine (VIALE C phase 3 randomised).

In the VIALE-A study, the most commonly occurring adverse reactions (≥20%) of any grade in patients receiving venetoclax in combination with azacitidine were thrombocytopenia, neutropenia, febrile neutropenia, nausea, diarrhoea, vomiting, anaemia, fatigue, pneumonia, hypokalaemia, and decreased appetite.

The most frequently reported serious adverse reactions (≥5%) in patients receiving venetoclax in combination with azacitidine were febrile neutropenia, pneumonia, sepsis and haemorrhage.
In the VIALE-C study, the most commonly occurring adverse reactions (≥20%) of any grade in patients receiving venetoclax in the combination with low dose cytarabine were neutropenia, thrombocytopenia, nausea, febrile neutropenia, anaemia, vomiting, diarrhoea, hypokalaemia, decreased appetite and pneumonia. The most frequently reported serious adverse reactions (≥5%) were febrile neutropenia, pneumonia and sepsis.

In the M14-358 study, the most commonly occurring adverse reactions (≥20%) of any grade in patients receiving venetoclax in combination with decitabine were thrombocytopenia, febrile neutropenia, nausea, haemorrhage, pneumonia, diarrhoea, fatigue, dizziness/syncope, vomiting, neutropenia, hypotension, hypokalaemia, decreased appetite, headache, abdominal pain, and anaemia. The most frequently reported serious adverse reactions (≥5%) were febrile neutropenia, pneumonia, bacteraemia and sepsis.

The 30-day mortality rate in the VIALE-A study was 7.4% (21/283) with venetoclax in combination with azacitidine and 6.3% (9/144) in the placebo with azacitidine arm.
The 30-day mortality rate in the VIALE-C study was 12.7% (18/142) with venetoclax in combination with low-dose cytarabine and 16.2% (11/68) in the placebo with low-dose cytarabine-arm.

The 30-day mortality rate in the M14-358 study with venetoclax in combination with decitabine was 6.5% (2/31).

Tabulated list of adverse reactions

Adverse reactions are listed below by MedDRA body system organ class 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 seriousness.

*Chronic lymphocytic leukaemia*
The frequencies of adverse reactions reported with Venclyxto, in combination with obinutuzumab, rituximab, or as monotherapy in patients with CLL are summarised in Table 8.

Table 8: Adverse drug reactions reported in patients with CLL treated with venetoclax

| System organ class | Frequency | All grades[a] | Grade ≥3[a] |
|---|---|---|---|
| **Infections and infestations** | Very common | Pneumonia<br>Upper respiratory tract infection | |
| | Common | Sepsis<br>Urinary tract infection | Sepsis<br>Pneumonia<br>Urinary tract infection<br>Upper respiratory tract infection |
| **Blood and lymphatic system disorders** | Very common | Neutropenia<br>Anaemia<br>Lymphopenia | Neutropenia<br>Anaemia |
| | Common | Febrile neutropenia | Febrile neutropenia<br>Lymphopenia |
| **Metabolism and nutrition disorders** | Very common | Hyperkalaemia<br>Hyperphosphataemia<br>Hypocalcaemia | |
| | Common | Tumour lysis syndrome<br>Hyperuricaemia | Tumour lysis syndrome<br>Hyperkalaemia<br>Hyperphosphataemia<br>Hypocalcaemia<br>Hyperuricaemia |
| **Gastrointestinal disorders** | Very common | Diarrhoea<br>Vomiting<br>Nausea<br>Constipation | |
| | Common | | Diarrhoea<br>Vomiting<br>Nausea |
| | Uncommon | | Constipation |
| **General disorders and administration site conditions** | Very common | Fatigue | |
| | Common | | Fatigue |
| **Investigations** | Common | Blood creatinine increased | |
| | Uncommon | | Blood creatinine increased |

[a]Only the highest frequency observed in the studies is reported (based on studies CLL14, MURANO, M13-982, M14-032, and M12-175).

*AMPLIFY*
When venetoclax is administered in combination with acalabrutinib, refer to the SmPC for acalabrutinib prior to initiation of treatment.

The adverse reactions observed with venetoclax in combination with acalabrutinib, with or without obinutuzumab, were consistent with those reported for each individual component of the respective combination regimens (see Table 8 and acalabrutinib SmPC).

Table 9 provides the adverse reactions reported in study CLL3011(GLOW). Adverse reactions are listed by MedDRA body system organ class, rate, and frequency.

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 Venetoclax Plus Ibrutinib Compared with Obinutuzumab Plus Chlorambucil in GLOW

| **Adverse Reaction by Body System** | **Venetoclax + Ibrutinib (N = 106)** | | **Obinutuzumab + Chlorambucil (N = 105)** | |
|---|---|---|---|---|
| | All Grades % (Frequency) | Grade 3 or 4 % | All Grades % | Grade 3 or 4 % |
| **Gastrointestinal disorders** | | | | |
| Diarrhea | 51 (Very common) | 10 | 12 | <1 |
| **General disorders and administration site conditions** | | | | |
| Fatigue | 15 (Very common) | <1 | 10 | 0 |
| **Infections & infestations** | | | | |
| Urinary tract infection | 16 (Very common) | 2 | 5 | 2 |
| Pneumonia[b] | 13 (Very common) | 7 | 10 | 5 |
| **Metabolism and nutrition disorders:** | | | | |
| Hyperphosphatemia | 10 (Very common) | <1 | <1 | 0 |
| [a]Includes pneumonia, bronchopulmonary aspergillosis, lung abscess, pneumonia cytomegaloviral, and pneumonia streptococcal. | | | | |

Other adverse reactions reported in the venetoclax + ibrutinib arm are presented below:
**Blood & lymphatic system disorders:** neutropenia[a] (42%), anemia (18%), febrile neutropenia (2%), lymphocyte count decreased (<1%)

**Gastrointestinal Disorders:** nausea (26%), vomiting (14%), constipation (10%)
**Infections & infestations:** upper respiratory tract infection (12%), sepsis[b] (<1%)
**Investigations:** blood creatinine increased (5%)
**Metabolism and nutrition disorders:** hyperkalemia[c] (9%), hyperuricemia[d] (7%), hypocalcemia[e] (4%)

[a]neutropenia and neutrophil count decreased.
[b]Includes septic shock.
[c]Includes hyperkalemia and blood potassium increased.
[d]Includes hyperuricemia and blood uric acid increased.
[e]Includes hypocalcemia and blood calcium decreased.

Table 10 provides the adverse reactions reported in 10% or more of patients in study PCYC-1142-CA (CAPTIVATE), listed by MedDRA body system organ class and rate.

Table 10: Summary of Adverse Reactions Reported with Incidence of ≥10% (all grade) in Patients Treated with Venetoclax Plus Ibrutinib in the FD and MRD (First 16 Cycles) Cohorts in CAPTIVATE

| **Adverse Reaction by Body System** | **Venetoclax + Ibrutinib N = 323** | |
|---|---|---|
| | All grades % | Grade 3 or 4 % |
| **Gastrointestinal disorders** | | |
| Diarrhea | 67 | 4 |
| Nausea | 44 | <1 |
| Vomiting | 22 | 1 |
| Constipation | 16 | 0 |
| **Blood & lymphatic system disorders** | | |
| Neutropenia[a] | 47 | 37 |
| **General disorders and administration site conditions** | | |
| Fatigue | 26 | 2 |
| **Infections and infestations** | | |
| Upper respiratory tract infection | 26 | 0 |
| [a]Includes neutropenia and neutrophil count decreased. | | |

Other adverse reactions reported in the CAPTIVATE study are presented below:
**Blood & lymphatic system disorders:** anemia (7%), febrile neutropenia (1%), lymphopenia[a] (<1%)
**Infections & infestations:** urinary tract infection (7%), pneumonia[b] (4%), sepsis[c] (1%)
**Investigations:** blood creatinine increased (6%)

**Metabolism and nutrition disorders:** hyperphosphatemia[d] (7%), hyperuricemia[e] (7%), hyperkalemia[f] (6%), hypocalcemia[g] (3%), tumor lysis syndrome (<1%; 1 patient in MRD [first 16 cycles] cohort)
[a]Includes lymphopenia and lymphocyte count decreased.
[b]Includes pneumonia, pleurisy viral, pneumonia bacterial.
[c]Includes bacteremia, disseminated varicella zoster virus infection, Escherichia bacteremia, staphylococcal bacteremia.
[d]Includes hyperphosphatemia and blood phosphorus increased.
[e]Includes hyperuricemia and blood uric acid increased.
[f]Includes hyperkalemia and blood potassium increased.
[g]Includes hypocalcemia and blood calcium decreased.

*Acute myeloid leukaemia*
The frequencies of adverse reactions reported with Venclyxto in combination with a hypomethylating agent or low dose cytarabine in patients with AML are summarised in Table 11.

Table 11: Adverse drug reactions reported in patients with AML treated with venetoclax

| System organ class | Frequency | All grades[a] | Grade ≥3[a] |
|---|---|---|---|
| **Infections and infestations** | Very common | Pneumonia[b]<br>Sepsis[b]<br>Urinary tract infection | Pneumonia[b]<br>Sepsis[b] |
| | Common | | Urinary tract infection |
| **Blood and lymphatic system disorders** | Very common | Neutropenia[b]<br>Febrile neutropenia<br>Anaemia[b]<br>Thrombocytopenia[b] | Neutropenia[b]<br>Febrile neutropenia<br>Anaemia[b]<br>Thrombocytopenia[b] |
| **Metabolism and nutrition disorders** | Very common | Hypokalaemia<br>Decreased appetite | Hypokalaemia |
| | Common | Tumour lysis syndrome | Decreased appetite<br>Tumour lysis syndrome |
| | | | |
| **Nervous System Disorders** | Very common | Dizziness/syncope[b]<br>Headache | |
| | Common | | Dizziness/syncope[b] |
| | Uncommon | | Headache |
| **Vascular Disorders** | Very common | Hypotension<br>Haemorrhage[b] | Haemorrhage[b] |
| | Common | | Hypotension |
| **Respiratory, thoracic, and mediastinal disorder** | Very common | Dyspnoea | |
| | Common | | Dyspnoea |
| **Gastrointestinal disorders** | Very common | Nausea<br>Diarrhoea<br>Vomiting<br>Stomatitis<br>Abdominal pain | |
| | Common | | Nausea<br>Diarrhoea<br>Vomiting |
| | Uncommon | | Stomatitis |
| **Hepatobiliary Disorders** | Common | Cholecystitis/cholelithiasis[b] | Cholecystitis/cholelithiasis[b] |
| **Musculoskeletal disorders and connective tissue disorders** | Very common | Arthralgia | |
| | Uncommon | | Arthralgia |
| **General disorders and administration site conditions** | Very common | Fatigue<br>Asthenia | |
| | Common | | Fatigue<br>Asthenia |

| | | | |
|---|---|---|---|
| **Investigations** | Very common | Weight decreased<br>Blood bilirubin increased | |
| | Common | | Weight decreased<br>Blood bilirubin increased |
| [a]Only the highest frequency observed in the studies is reported (based on studies VIALE-A, VIALE C and M14-358).<br>[b]Includes multiple adverse reaction terms. | | | |

*Discontinuation and dose reductions due to adverse reactions*

Chronic lymphocytic leukaemia

Discontinuations due to adverse reactions in the AMPLIFY study occurred in 20% and 8% of patients treated with venetoclax in combination with acalabrutinib with or without obinutuzumab, respectively. Discontinuations due to adverse reactions occurred in 16% of patients treated with venetoclax in combination with obinutuzumab or rituximab in the CLL14 and MURANO studies, respectively. In the monotherapy studies with venetoclax, 11% of patients discontinued due to adverse reactions.

Dosage reductions due to adverse reactions in the AMPLIFY study occurred in 21% and 14% of patients treated with venetoclax in combination with acalabrutinib with or without obinutuzumab, respectively. Dosage reductions due to adverse reactions occurred in 21% of patients treated with the combination of venetoclax and obinutuzumab in the CLL14 study, in 15% of patients treated with the combination of venetoclax and rituximab in the MURANO study and in 14% of patients treated with venetoclax in the monotherapy studies.

Dose interruptions due to adverse reactions in the AMPLIFY study occurred in 65% and 50% of patients treated with venetoclax in combination with acalabrutinib with or without obinutuzumab, respectively. The most common adverse reaction that led to dose interruption of venetoclax in the AMPLIFY study was neutropenia (33% and 26% with or without obinutuzumab, respectively). Dose interruptions due to adverse reactions occurred in 74% of patients treated with the combination of venetoclax and obinutuzumab in the CLL14 study and in 71% of patients treated with the combination of venetoclax and rituximab in the MURANO study; the most common adverse reaction that led to dose interruption of venetoclax was neutropenia (41% and 43% in the CLL14 and MURANO studies, respectively). In the monotherapy studies with venetoclax, dose interruptions due to adverse reactions occurred in 40% of patients; the most common adverse reaction leading to dose interruption was neutropenia (5%).

Acute myeloid leukaemia
*Venetoclax in combination with a hypomethylating agent*

In the VIALE-A study, discontinuations of venetoclax due to adverse reactions occurred in 24% of patients treated with the combination of venetoclax and

azacitidine. Venetoclax dosage reductions due to adverse reactions occurred in 2% of patients. Venetoclax dose interruptions due to adverse reactions occurred in 72% of patients. Among patients who achieved bone marrow clearance of leukaemia, 53% underwent dose interruptions for ANC <500/microlitre. The most common adverse reaction that led to dose interruption (>10%) of venetoclax were febrile neutropenia, neutropenia, pneumonia, and thrombocytopenia.

In the M14-358 study, discontinuations due to adverse reactions occurred in 26% of patients treated with the combination of venetoclax and decitabine. Dosage reductions due to adverse reactions occurred in 6% of patients. Dose interruptions due to adverse reactions occurred in 65% of patients; the most common adverse reactions that led to dose interruption (≥5%) of venetoclax were febrile neutropenia, neutropenia/neutrophil count decreased, pneumonia, platelet count decreased, and white blood cell count decreased.

*Venetoclax in combination with low-dose cytarabine in randomised study (VIALE-C)*

In the VIALE-C study, discontinuations of venetoclax due to adverse reactions occurred in 26% of patients treated with the combination of venetoclax and low-dose cytarabine. Venetoclax dosage reductions due to adverse reactions occurred in 10% of patients. Venetoclax dose interruptions due to adverse reactions occurred in 63% of patients. Among patients who achieved bone marrow clearance of leukaemia, 37% underwent dose interruptions for ANC <500/ L. The most common adverse reactions that led to dose interruption (>5%) of venetoclax were neutropenia, thrombocytopenia, pneumonia febrile neutropenia, and anaemia.

Description of selected adverse reactions

*Tumour lysis syndrome*

Tumour lysis syndrome is an important identified risk when initiating venetoclax.

Chronic lymphocytic leukaemia

In the initial Phase 1 dose-finding studies, which had a shorter (2 to 3 week) 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. In venetoclax clinical studies, 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 titration phase (see section 4.2).

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 or ALC ≥25 x $10^9$/l. 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.

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 incorporate the current TLS prophylaxis and monitoring measures described in Posology (see section 4.2). All events of TLS occurred during the venetoclax 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 venetoclax. No clinical TLS was observed in patients who followed the current 5-week dose-titration schedule and TLS prophylaxis and monitoring measures (see section 4.2). The rates of grade ≥3 laboratory abnormalities relevant to TLS were hyperkalaemia 1%, hyperphosphataemia 1%, and hyperuricaemia 1%.

In the open-label, randomised phase 3 study (CLL14), the incidence of TLS was 1.4% (3/212) in patients treated with venetoclax + obinutuzumab. 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.

In the open-label, randomised phase 3 study (AMPLIFY), the incidence of TLS was 0.3% (1/291) in patients treated with venetoclax + acalabrutinib, and 0.4% (1/284) in patients treated with
venetoclax + acalabrutinib + obinutuzumab. Obinutuzumab administration was delayed in response to the TLS event. Both cases were laboratory TLS that resolved and did not lead to withdrawal from the study.

No adverse event of TLS was observed in the randomized phase 3 GLOW study.

The incidence of laboratory TLS was 0.3% (1/323) in the single-arm phase 2 CAPTIVATE study, reported in one patient in the MRD-guided cohort.

During post-marketing surveillance, TLS, including fatal events, has been reported after a single 20 mg dose of venetoclax (see sections 4.2 and 4.4).

Acute myeloid leukaemia

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) with venetoclax in combination with low dose cytarabine 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 a dose-titration schedule in addition to standard prophylaxis and monitoring measures (see section 4.2). All cases of TLS occurred during dose-titration.

In M14-358 study, no events of laboratory or clinical TLS were reported with venetoclax in combination with decitabine.

*Neutropenia and infections*
Neutropenia is an identified risk with Venclyxto treatment.

Chronic lymphocytic leukaemia

In the AMPLIFY study, neutropenia/neutrophil count decreased/febrile neutropenia (all grades) was reported in 37% of patients in the venetoclax + acalabrutinib arm. Dose interruption occurred in 26% of patients and 0.7% of patients discontinued venetoclax due to neutropenia/neutrophil count decreased/febrile neutropenia. Grade ≥3 neutropenia/neutrophil count decreased/febrile neutropenia was reported in 32% of patients. Grade ≥3 infections were reported in 12% and serious infections in 12% of patients.

In the AMPLIFY study, neutropenia/neutrophil count decreased/febrile neutropenia (all grades) was reported in 50% of patients in the venetoclax + acalabrutinib + obinutuzumab arm. Dose interruption occurred in 33% of patients and 1% of patients discontinued venetoclax due to neutropenia/neutrophil count decreased/febrile neutropenia. Grade ≥3 neutropenia/neutrophil count decreased/febrile neutropenia was reported in 46% of patients. Grade ≥3 infections were reported in 24% and serious infections in 24% of patients.

In the CLL14 study, neutropenia (all grades) was reported in 58% of patients in the venetoclax + obinutuzumab arm; 41% of patients treated with venetoclax + obinutuzumab experienced dose interruption and 2% of patients 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). Febrile neutropenia was reported in 6% of patients, grade ≥3 infections in 19%, and serious infections in 19% of patients. Deaths due to infection occurred in 1.9% of patients while on treatment and 1.9% of patients following treatment discontinuation.
In the MURANO study, neutropenia (all grades) was reported in 61% of patients in 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 to 712 days). With venetoclax + rituximab treatment, febrile neutropenia was reported in 4% of patients, grade ≥3 infections in 18%, and serious infections in 21% of patients.

In the venetoclax + ibrutinib arm in the GLOW study, neutropenia (all grades) was reported in 42% of patients; grade 3 or 4 neutropenia was reported in 35% of patients. Nineteen percent experienced dose interruption and 8% had dose reduction due to neutropenia. In the venetoclax + ibrutinib arm versus the obinutuzumab + chlorambucil arm, respectively, the following were reported: febrile neutropenia 2% versus 3%, grade ≥3 infections 7% versus 9%, and serious infections 12% versus 9%.

In the CAPTIVATE study, neutropenia (all grades) was reported in 47% of patients in the venetoclax + ibrutinib arm; grade 3 or 4 neutropenia was reported in 37% of patients. Fourteen percent experienced dose interruption, 4% had dose reduction and 1 patient (0.3%) discontinued venetoclax due to neutropenia. Febrile neutropenia was reported in 1%, grade ≥3 infections in 8%, and serious infections in 8% of patients.

Acute myeloid leukaemia
In the VIALE-A study, grade ≥3 neutropenia was reported in 45% of patients. The following were also 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%.

In the M14-358 study, neutropenia was reported in 35% (all grades) and 35% (grade 3 or 4) of patients in the venetoclax + decitabine arm.

In the VIALE-C study, grade ≥3 neutropenia was reported in 53% of patients. The following were also 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%.

Paediatric population
The safety profile of venetoclax in paediatric patients is based on data from an open-label phase 1 study (M13-833) in 140 paediatric and young adult patients with relapsed or refractory malignancies (see section 5.1). No new risks or safety concerns were identified in the study.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme:
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 4.9 Overdose

There is no specific antidote for venetoclax. Patients who experience overdose should be closely monitored and appropriate supportive treatment provided. During dose-titration phase, treatment should be interrupted, and patients should be monitored carefully for signs and symptoms of TLS (fever, chills, nausea, vomiting, confusion, shortness of breath, seizures, irregular heartbeat, dark or cloudy urine, unusual tiredness, muscle or joint pain, abdominal pain, and distension) along with other toxicities (see section 4.2). Dialysis does not result in removal of venetoclax.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, other antineoplastic agents, ATC code: L01XX52

Mechanism of action

Venetoclax is a potent, selective inhibitor of B-cell lymphoma (BCL)-2, an anti-apoptotic protein. Overexpression of BCL-2 has been demonstrated in CLL and AML cells where it mediates tumour cell survival and has been associated with resistance to chemotherapeutics. Venetoclax binds directly to the BH3-binding groove of BCL-2, displacing BH3 motif-containing pro-apoptotic proteins like BIM, to initiate mitochondrial outer membrane permeabilization (MOMP), caspase activation, and programmed cell death. In non-clinical studies, venetoclax has demonstrated cytotoxic activity in tumour cells that overexpress BCL-2.

Pharmacodynamic effects

*Cardiac electrophysiology*

The effect of multiple doses of venetoclax up to 1200 mg once daily on the QTc interval was evaluated in an open-label, single-arm study in 176 patients. Venetoclax 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*

*Venetoclax in combination with acalabrutinib with or without obinutuzumab for the treatment of patients with previously untreated CLL – study ACE-CL-311 (AMPLIFY)*

A randomised (1:1:1), multi-centre, open-label Phase 3 study of 867 patients evaluated the safety and efficacy of venetoclax + acalabrutinib versus venetoclax + acalabrutinib + obinutuzumab versus Investigator's choice of chemoimmunotherapy, either FCR (fludarabine plus cyclophosphamide plus rituximab) or BR (bendamustine plus rituximab) in patients with previously untreated CLL. AMPLIFY included patients previously untreated for CLL without del(17p) or TP53 mutation that were 18 years of age and older. The

trial allowed patients to receive antithrombotic agents except warfarin and other vitamin K antagonists.

Patients were randomised in a 1:1:1 ratio into 3 arms to receive:

- Venetoclax + acalabrutinib: Acalabrutinib 100 mg was administered twice daily starting on Cycle 1 Day 1 for a total of 14 cycles or until disease progression or unacceptable toxicity. On Cycle 3 Day 1, patients started the venetoclax 5-week dose-titration schedule, starting at 20 mg and increasing weekly to 50 mg, 100 mg, 200 mg and finally 400 mg once daily. Venetoclax was administered for a total of 12 cycles. Each cycle was 28 days.

- Venetoclax + acalabrutinib + obinutuzumab: Acalabrutinib 100 mg was administered twice daily starting on Cycle 1 Day 1 for a total of 14 cycles or until disease progression or unacceptable toxicity. On Cycle 3 Day 1, patients started the venetoclax 5-week dose-titration schedule, starting at 20 mg and increasing weekly to 50 mg, 100 mg, 200 mg and finally 400 mg once daily. Venetoclax was administered for a total of 12 cycles. Obinutuzumab 1 000 mg was administered on Day 1 or Day 1 and 2 (100 mg on Day 1 and 900 mg on Day 1 or 2), 8 and 15 of Cycle 2 followed by 1 000 mg on Day 1 of Cycles 3-7. Each cycle was 28 days.

- Investigator's choice of chemoimmunotherapy (FCR/BR):
    - Fludarabine plus cyclophosphamyde plus rituximab (FCR): Fludarabine (25 mg/m$^2$) and cyclophosphamide (250 mg/m$^2$) were administered on Days 1-3 up to a maximum of 6 cycles. Rituximab was administered at a dose of 375 mg/m$^2$ on Day 1 Cycle 1 and 500 mg/m$^2$ on Day 1 of Cycles 2 up to 6. Each cycle was 28 days.
    - Bendamustine plus rituximab (BR): Bendamustine 90 mg/m$^2$ was administered on Days 1 and 2 up to maximum of 6 cycles. Rituximab was administered at a dose of 375 mg/m$^2$ on Day 1 Cycle 1 and 500 mg/m$^2$ on Day 1 of Cycles 2 up to 6. Each cycle was 28 days.

Patients were stratified by age (>65 years or ≤65 years), IGHV mutational status (mutated versus unmutated), Rai stage (high risk [≥3] versus non-high risk) and geographic region (North America versus Western Europe versus other). Table 10 summarises the baseline demographics and disease characteristics of the study population.

Table 10: Baseline patient characteristics in (AMPLIFY) patients with previously untreated CLL

| Characteristic | **Venetoclax + acalabrutinib N=291** | **Venetoclax + acalabrutinib + obinutuzumab N=286** | **FCR/BR N=290** |
|---|---|---|---|
| Age, years; median (range) | 61 (31-84) | 61 (29-81) | 61 (26-86) |
| Male; % | 61.2 | 69.2 | 63.1 |
| Caucasian; % | 91.1 | 86.7 | 86.9 |
| ECOG performance status 0-1; % | 90.0 | 95.1 | 90.3 |
| Median time from diagnosis to randomisation (months) | 28.5 | 26.1 | 29.6 |
| Bulky disease with nodes ≥ 5 cm; % | 38.8 | 35.0 | 42.8 |
| Cytogenetics/FISH Category; % | | | |
| 11q deletion | 17.5 | 19.6 | 15.9 |
| Complex karyotype (≥ 3 abnormalities) | 15.5 | 16.1 | 14.5 |
| Unmutated IGHV; % | 57.4 | 59.1 | 59.3 |
| Rai stage; % | | | |
| 0 | 1.0 | 0.3 | 1.4 |
| I | 16.2 | 21.3 | 21.4 |
| II | 35.7 | 37.8 | 33.4 |
| III | 23.7 | 17.8 | 20.3 |
| IV | 23.4 | 22.7 | 23.4 |

The primary endpoint was IRC-assessed PFS for venetoclax + acalabrutinib versus Investigator's choice of chemoimmunotherapy (FCR/BR) arm as assessed by IWCLL 2018 criteria. Additional efficacy endpoints were IRC-assessed PFS of venetoclax + acalabrutinib + obinutuzumab versus Investigator's choice (FCR/BR) arm and OS in both venetoclax + acalabrutinib arm vs. Investigator's choice (FCR/BR) arm and venetoclax + acalabrutinib + obinutuzumab vs. Investigator's choice (FCR/BR) arm.

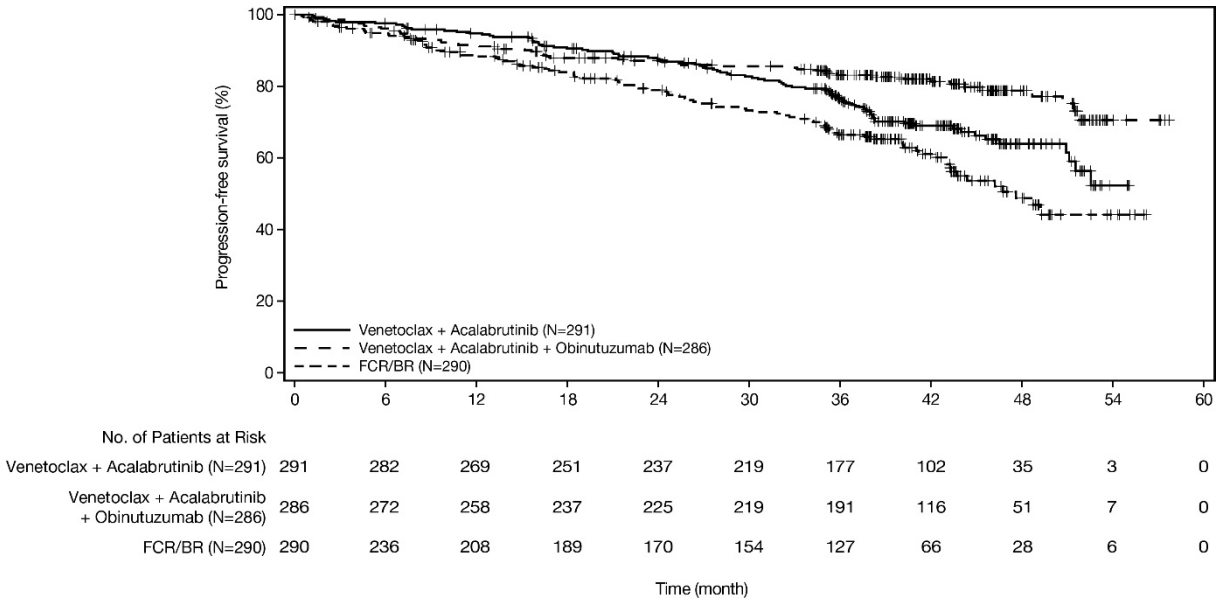
Efficacy results are presented in Table 11. The Kaplan-Meier curve for IRC-PFS is shown in Figure 1.

Table 11: Efficacy results in (AMPLIFY) patients with previously untreated CLL

| | Venetoclax + acalabrutinib N=291 | Venetoclax + acalabrutinib + obinutuzumab N=286 | FCR/BR[a] N=290 |
|---|---|---|---|
| **Progression-free survival**[*] | | | |
| Number of events (%) | 89 (30.6) | 56 (19.6) | 95 (32.8) |
| PD, n (%) | 77 (26.5) | 23 (8.0) | 66 (22.8) |
| Death events (%) | 12 (4.1) | 33 (11.5) | 29 (10.0) |
| Median (95% CI), months | NE (51.1, NE) | NE (NE, NE) | 47.6 (43.3, NE) |
| HR[†] (95% CI) | 0.65 (0.49, 0.87) | 0.42 (0.30, 0.59) | - |
| P-value | 0.0038 | 0.0001 | - |
| **Overall survival**[b] | | | |
| Death events (%) | 23 (7.9) | 37 (12.9) | 44 (15.2) |
| HR[†] (95% CI) | 0.42 (0.25, 0.70)[c] | 0.75 (0.48, 1.16) | - |

CI= confidence interval; NE= not evaluable; PD = Progressive disease.
[*]Per IRC assessment.
[†]Based on stratified Cox-Proportional-Hazards model.
[a]Per Investigator's choice 143 patients were planned to receive FCR and 147 patients were planned to receive BR.
[b]OS data at additional 6 months follow-up from PFS interim analysis.
[c]The p-value is not significant after adjusting for multiplicity.

Figure 1: Kaplan-Meier curve of IRC-assessed progression-free survival (intent-to-treat population) in AMPLIFY




*Venetoclax in combination with obinutuzumab for the treatment of patients with previously untreated CLL – study BO25323 (CLL14)*
A randomised (1:1), multicentre, open-label phase 3 study evaluated the efficacy and safety of venetoclax + obinutuzumab versus obinutuzumab + chlorambucil in patients with previously untreated CLL and comorbidities (total CIRS score >6 or creatinine clearance [CrCl] <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 100 mg on Cycle 1 Day 1, followed by 900 mg which could have been administered on Day 1 or Day 2, then 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 venetoclax dose-titration schedule, continuing through Cycle 2 Day 28. Upon completion of the dose-titration schedule, patients continued venetoclax 400 mg once daily from Cycle 3 Day 1 until the last day of Cycle 12. Each cycle was 28 days. Patients randomised to the obinutuzumab + chlorambucil arm received 0.5 mg/kg oral chlorambucil on Day 1 and Day 15 of Cycles 1-12. Patients continued to be followed for disease progression and overall survival (OS) after completing therapy.

Baseline demographic and disease characteristics were similar between the study arms. The median age was 72 years (range: 41 to 89 years), 89% were white, and 67% were male; 36% and 43% were Binet stage B and C, respectively. The median CIRS score was 8.0 (range: 0 to 28) and 58% of patients had CrCl <70 ml/min. A 17p deletion was detected in 8% of patients, *TP53* mutations in 10%, 11q deletion in 19%, and unmutated *IgVH* in 57%. The median follow-up at the time of the primary analysis was 28 months (range: 0 to 36 months).

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 had decreased to 1.03 x $10^9$ cells/l (range: 0.2 to 43.4 x $10^9$ cells/l) in the obinutuzumab + chlorambucil arm and 1.27 x $10^9$ cells/l (range: 0.2 to 83.7 x $10^9$ cells/l) in the venetoclax + obinutuzumab arm.

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

At the time of the primary analysis (data cut-off date 17 August 2018), 14% (30/216) of patients in the venetoclax + obinutuzumab arm had a PFS event of disease progression or death compared with 36% (77/216) in the obinutuzumab + chlorambucil arm, as assessed by investigators (hazard ratio [HR]: 0.35 [95% confidence interval [CI]: 0.23, 0.53]; p<0.0001, stratified log-rank test). Median PFS was not reached in either study arm.

Progression-free survival was also assessed by an Independent Review Committee (IRC) and was consistent with the investigator-assessed PFS.

Investigator-assessed overall response rate (ORR) was 85% (95% CI: 79.2, 89.2) and 71% (95% CI: 64.8, 77.2) in the venetoclax + obinutuzumab and obinutuzumab + chlorambucil arms, respectively (p=0.0007, Cochran-Mantel-Haenszel test). Investigator-assessed complete remission + complete remission with incomplete marrow recovery (CR + CRi) rate was 50% and 23% in the venetoclax + obinutuzumab and obinutuzumab + chlorambucil arms, respectively (p<0.0001, Cochran-Mantel-Haenszel test).

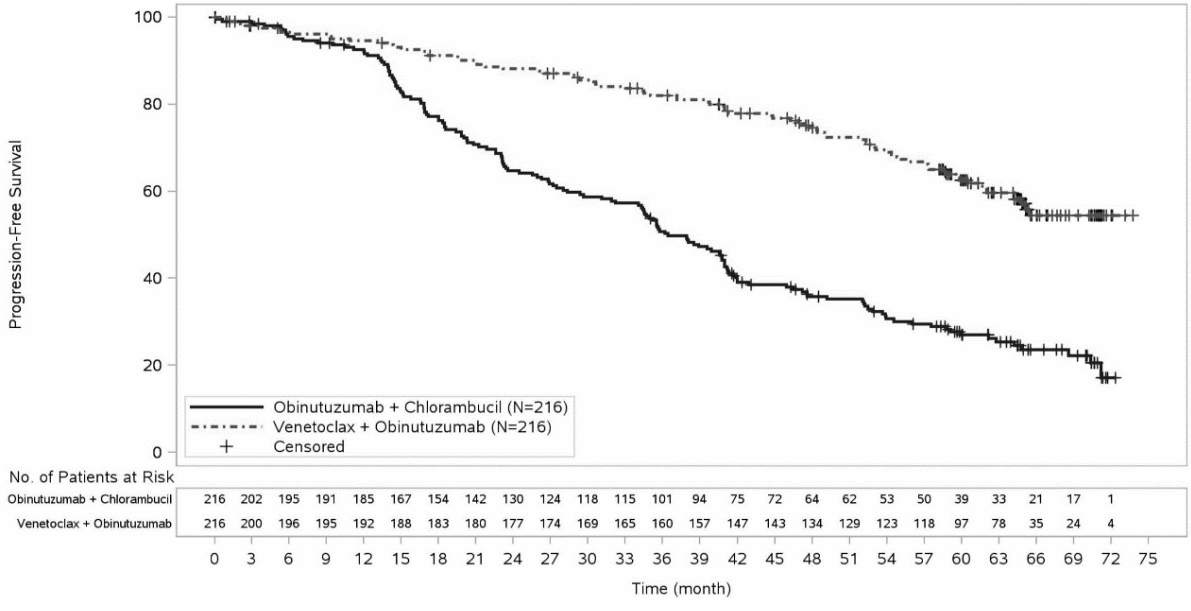
Minimal residual disease (MRD) at the end of treatment was evaluated using allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) assay. MRD negativity was defined as less than one CLL cell per $10^4$ leukocytes. MRD negativity rates in peripheral blood were 76% (95% CI: 69.2, 81.1) in the venetoclax + obinutuzumab arm compared to 35% (95% CI: 28.8, 42.0) in the obinutuzumab + chlorambucil arm (p<0.0001). Per protocol, MRD in bone marrow was to be assessed only in responding patients (CR/CRi and partial remission [PR]). MRD negativity rates in the bone marrow were 57% (95% CI: 50.1, 63.6) in the venetoclax + obinutuzumab arm and 17% (95% CI: 12.4, 22.8) in the obinutuzumab + chlorambucil arm (p<0.0001).

*65-month follow-up*
Efficacy was assessed after a median follow-up of 65 months (data cut-off date 8 November 2021). Efficacy results for the CLL14 65-month follow-up are presented in Table 12. The Kaplan-Meier curve of investigator-assessed PFS is shown in Figure 2.

Table 12: Investigator-assessed efficacy results in CLL14 (65-month follow-up)

| **Endpoint** | **Venetoclax + obinutuzumab N = 216** | **Obinutuzumab + chlorambucil N = 216** |
|---|---|---|
| Progression-free survival | | |
| Number of events (%) | 80 (37) | 150 (69) |
| Median, months (95% CI) | NR (64.8, NE) | 36.4 (34.1, 41.0) |
| Hazard ratio, stratified (95% CI) | 0.35 (0.26, 0.46) | |
| Overall survival | | |
| Number of events (%) | 40 (19) | 57 (26) |
| Hazard ratio, stratified (95% CI) | 0.72 (0.48, 1.09) | |
| CI = confidence interval; NE = not evaluable; NR = not reached | | |

Figure 2: Kaplan-Meier curve of investigator-assessed progression-free survival (intent-to-treat population) in CLL14 with 65-month follow-up



The PFS benefit with venetoclax + obinutuzumab versus obinutuzumab + chlorambucil treatment was observed across all subgroups of patients evaluated, including high-risk patients with deletion 17p and/or *TP53* mutation and/or unmutated *IgVH*.

*Venetoclax in combination with rituximab for the treatment of patients with CLL who have received at least one prior therapy – study GO28667 (MURANO)*

A randomised (1:1), multicentre, open-label phase 3 study evaluated the efficacy and safety of venetoclax + rituximab versus bendamustine + rituximab in patients with previously treated CLL. Patients in the venetoclax + rituximab arm completed the Venclyxto 5-week dose-titration schedule and then received 400 mg once daily for 24 months 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 schedule 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 as described above.

Median age was 65 years (range: 22 to 85); 74% were male, and 97% were white. Median time since diagnosis was 6.7 years (range: 0.3 to 29.5). Median prior lines of therapy was 1 (range: 1 to 5); and included alkylating agents (94%), anti-CD20 antibodies (77%), B-cell receptor pathway inhibitors (2%) and prior purine analogues (81%, including 55% fludarabine + cyclophosphamide + rituximab (FCR)). At baseline, 47% of patients had one or more nodes ≥5 cm, and 68% had ALC ≥25 x 10$^9$/l. A 17p deletion was detected in 27% of patients, *TP53* mutations in 26%, 11q deletion in 37%, and unmutated *IgVH* gene in 68%. Median follow-up time for primary analysis was 23.8 months (range: 0.0 to 37.4 months).

Progression-free survival was assessed by investigators using the IWCLL updated NCI-WG guidelines (2008).

At the time of the primary analysis (data cut-off date 8 May 2017), 16% (32/194) of patients in the venetoclax + rituximab arm had experienced a PFS event, compared with 58% (114/195) in the bendamustine + rituximab arm (HR: 0.17 [95% CI: 0.11, 0.25]; p<0.0001, stratified log-rank test). The PFS events included 21 disease progression and 11 death events in the venetoclax + rituximab arm, and 98 disease progression and 16 death events in the bendamustine + rituximab arm. Median PFS was not reached in the venetoclax + rituximab arm and was 17.0 months (95% CI: 15.5, 21.6) in the bendamustine + rituximab arm.

The 12- and 24-month PFS estimates were 93% (95% CI: 89.1, 96.4) and 85% (95% CI: 79.1, 90.6) in the venetoclax + rituximab arm and 73%(95% CI: 65.9, 79.1) and 36% (95% CI: 28.5, 44.0) in the bendamustine + rituximab arm, respectively.

Efficacy results for the primary analysis were also assessed by an IRC demonstrating a statistically significant 81% reduction in the risk of progression or death for patients treated with venetoclax + rituximab (HR: 0.19 [95% CI: 0.13, 0.28]; p<0.0001).

Investigator-assessed overall response rate (ORR) for patients treated with venetoclax + rituximab was 93% (95% CI: 88.8, 96.4), with a complete remission (CR) + complete remission with incomplete marrow recovery (CRi) rate of 27%, nodular partial remission (nPR) rate of 3%, and partial remission (PR) rate of 63%. For patients treated with bendamustine + rituximab, ORR was 68% (95% CI: 60.6, 74.2), with a CR + CRi rate of 8%, nPR rate of 6%, and PR rate of 53%. Median duration of response (DOR) was not reached with median follow-up of approximately 23.8 months. The IRC-assessed ORR for patients treated with venetoclax + rituximab was 92% (95% CI: 87.6, 95.6), with a CR + CRi rate of 8%, nPR rate of 2%, and PR rate of 82%. For patients treated with bendamustine + rituximab, IRC-assessed ORR was 72% (95% CI: 65.5, 78.5), with a CR + CRi rate of 4%, nPR rate of 1%, and PR rate of 68%. The discrepancy between IRC- and investigator-assessed CR rates was 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.

MRD at the end of combination treatment was evaluated using ASO-PCR and/or flow cytometry. MRD negativity was defined as less than one CLL cell per $10^4$ leukocytes. MRD negativity rates in peripheral blood were 62% (95% CI: 55.2, 69.2) in the venetoclax + rituximab arm compared to 13% (95% CI: 8.9, 18.9) in the bendamustine + rituximab arm. Of those with MRD assay results available in peripheral blood, 72% (121/167) in the venetoclax + rituximab arm and 20% (26/128) in the bendamustine + rituximab arm were found to be MRD negative. MRD negativity rates in the bone marrow were 16% (95% CI: 10.7, 21.3) in the venetoclax + rituximab arm and 1% (95% CI: 0.1, 3.7) in the bendamustine + rituximab arm. Of those with MRD assay results available in bone marrow, 77% (30/39) in the venetoclax + rituximab arm and 7% (2/30) in the bendamustine + rituximab arm were found to be MRD negative.

Median OS had not been reached in either treatment arm. Death occurred in 8% (15/194) of patients treated with venetoclax + rituximab and 14% (27/195) of patients treated with bendamustine + rituximab (hazard ratio: 0.48 [95% CI: 0.25, 0.90]).

By the data cut-off date, 12% (23/194) of patients in the venetoclax + rituximab arm and 43% (83/195) of patients in the bendamustine + rituximab arm had started a new anti-leukaemic treatment or died (stratified hazard ratio: 0.19; [95% CI: 0.12, 0.31]). The median time to new anti-leukaemic treatment or death was not reached in the venetoclax + rituximab arm and was 26.4 months in the bendamustine + rituximab arm.

*59-month follow-up*

Efficacy was assessed after a median follow-up of 59 months (data cut-off date 8 May 2020). Efficacy results for the MURANO 59-month follow-up are presented in Table 13.

Table 13: Investigator-assessed efficacy results in MURANO (59-month follow-up)

| **Endpoint** | **Venetoclax + rituximab N = 194** | **Bendamustine + rituximab N = 195** |
|---|---|---|
| Progression-free survival | | |
| Number of events (%)[a] | 101 (52) | 167 (86) |
| Median, months (95% CI) | 54 (48.4, 57.0) | 17 (15.5, 21.7) |
| Hazard ratio, stratified (95% CI) | 0.19 (0.15, 0.26) | |
| Overall survival | | |
| Number of events (%) | 32 (16) | 64 (33) |
| Hazard ratio (95% CI) | 0.40 (0.26, 0.62) | |
| 60-month estimate, % (95% CI) | 82 (76.4, 87.8) | 62 (54.8, 69.6) |
| Time to next anti-leukaemic treatment | | |
| Number of events (%)[b] | 89 (46) | 149 (76) |
| Median, months (95% CI) | 58 (55.1, NE) | 24 (20.7, 29.5) |
| Hazard ratio, stratified (95% CI) | 0.26 (0.20, 0.35) | |
| MRD negativity[c] | | |
| Peripheral blood at end of treatment, n (%)[d] | 83 (64) | NA[f] |
| 3-year PFS estimate from end of treatment, % (95% CI)[e] | 61 (47.3, 75.2) | NA[f] |
| 3-year OS estimate from end of treatment, % (95% CI)[e] | 95 (90.0, 100.0) | NA[f] |

CI= confidence interval; MRD = minimal residual disease; NE = not evaluable; OS= overall survival; PFS = progression-free survival; NA = not applicable.

[a]87 and 14 events in the venetoclax + rituximab arm were due to disease progression and death, compared to 148 and 19 events in the bendamustine + rituximab arm, respectively.

[b]68 and 21 events in the venetoclax + rituximab arm were due to patients starting a new anti-leukaemic treatment and death, compared to 123 and 26 events in the bendamustine + rituximab arm, respectively.

[c]Minimal residual disease was evaluated using allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) and/or flow cytometry. The cut-off for a negative status was one CLL cell per $10^4$ leukocytes.

[d]In patients who completed venetoclax treatment without progression (130 patients).

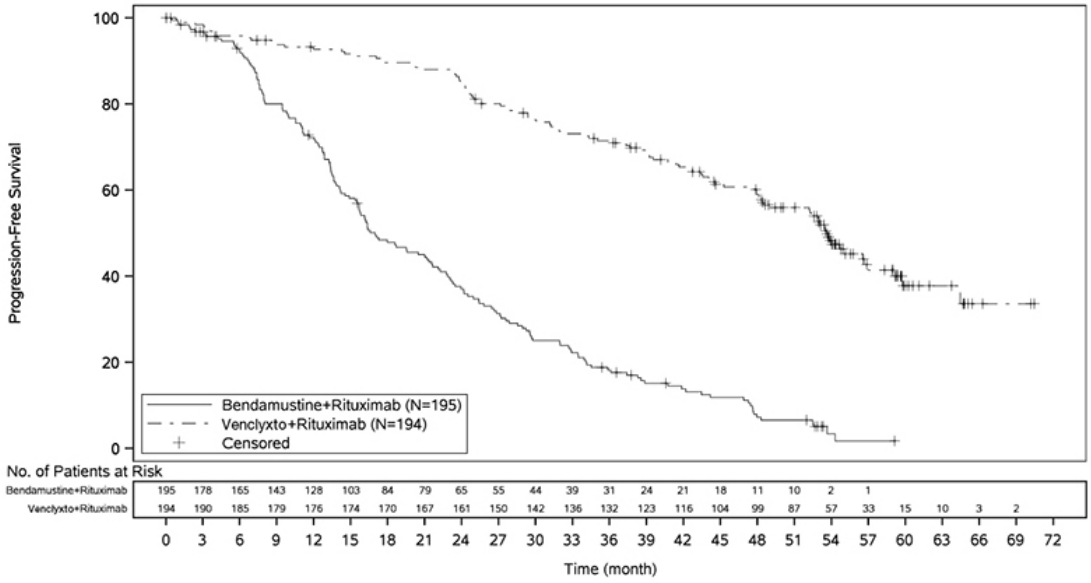
[e]In patients who completed venetoclax treatment without progression and were MRD negative (83 patients).

[f]No equivalent to end of treatment visit in bendamustine + rituximab arm.

In total, 130 patients in the venetoclax + rituximab arm completed 2 years of venetoclax treatment without progression. For these patients, the 3-year PFS estimate post-treatment was 51% (95 % CI: 40.2, 61.9).

The Kaplan-Meier curve of investigator-assessed PFS is shown in Figure 3.

Figure 3: Kaplan-Meier curve of investigator-assessed progression-free survival (intent-to-treat population) in MURANO (data cut-off date 8 May 2020) with 59-month follow-up

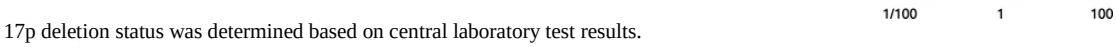



## Results of subgroup analyses

The observed PFS benefit of venetoclax + rituximab compared with bendamustine + rituximab was consistently observed across all subgroups of patients evaluated, including high-risk patients with deletion 17p/*TP53* mutation and/or unmutated *IgVH* (Figure 4).

Figure 4: Forest plot of investigator-assessed progression-free survival in subgroups from MURANO (data cut-off date 8 May 2020) with 59-month follow-up

| Subgroups | Total n | Bendamustine+ Rituximab (N=195) n | Bendamustine+ Rituximab (N=195) Median (Months) | Venetoclax+ Rituximab (N=194) n | Venetoclax+ Rituximab (N=194) Median (Months) | Hazard Ratio | 95% Wald CI |
|---|---|---|---|---|---|---|---|
| **All Patients** | 389 | 195 | 17.0 | 194 | 53.6 | 0.21 | (0.16, 0.27) |
| **Chromosome 17p Deletion (central)** | | | | | | | |
| Normal | 250 | 123 | 21.6 | 127 | 55.1 | 0.19 | (0.13, 0.27) |
| Abnormal | 92 | 46 | 14.6 | 46 | 47.9 | 0.27 | (0.16, 0.45) |
| **p53 Mutation and/or 17p Deletion (central)** | | | | | | | |
| Unmutated | 201 | 95 | 22.9 | 106 | 56.6 | 0.18 | (0.12, 0.26) |
| Mutated | 147 | 75 | 14.2 | 72 | 45.3 | 0.26 | (0.17, 0.38) |
| **Age Group 65 (yr)** | | | | | | | |
| < 65 | 186 | 89 | 15.4 | 97 | 49.0 | 0.20 | (0.14, 0.29) |
| >= 65 | 203 | 106 | 21.7 | 97 | 57.0 | 0.20 | (0.14, 0.30) |
| **Age Group 75 (yr)** | | | | | | | |
| < 75 | 336 | 171 | 16.4 | 165 | 53.5 | 0.21 | (0.16, 0.28) |
| >= 75 | 53 | 24 | 20.0 | 29 | 64.5 | 0.24 | (0.12, 0.51) |
| **Number of Prior Regimens** | | | | | | | |
| 1 | 228 | 117 | 16.4 | 111 | 54.0 | 0.18 | (0.13, 0.26) |
| > 1 | 161 | 78 | 18.6 | 83 | 53.1 | 0.25 | (0.17, 0.38) |
| **Bulky Disease (Lymph Nodes with the Largest Diameter)** | | | | | | | |
| < 5 cm | 197 | 97 | 16.6 | 100 | 53.8 | 0.21 | (0.14, 0.30) |
| >= 5 cm | 172 | 88 | 15.8 | 84 | 48.4 | 0.19 | (0.13, 0.29) |
| **Baseline IgVH Mutation Status** | | | | | | | |
| Mutated | 104 | 51 | 24.2 | 53 | NE | 0.14 | (0.07, 0.26) |
| Unmutated | 246 | 123 | 15.7 | 123 | 52.2 | 0.19 | (0.13, 0.26) |
| **Refractory vs. Relapse to Most Recent Prior Therapy** | | | | | | | |
| Refractory | 59 | 29 | 13.6 | 30 | 31.9 | 0.34 | (0.17, 0.66) |
| Relapse | 330 | 166 | 18.6 | 164 | 53.8 | 0.19 | (0.14, 0.25) |

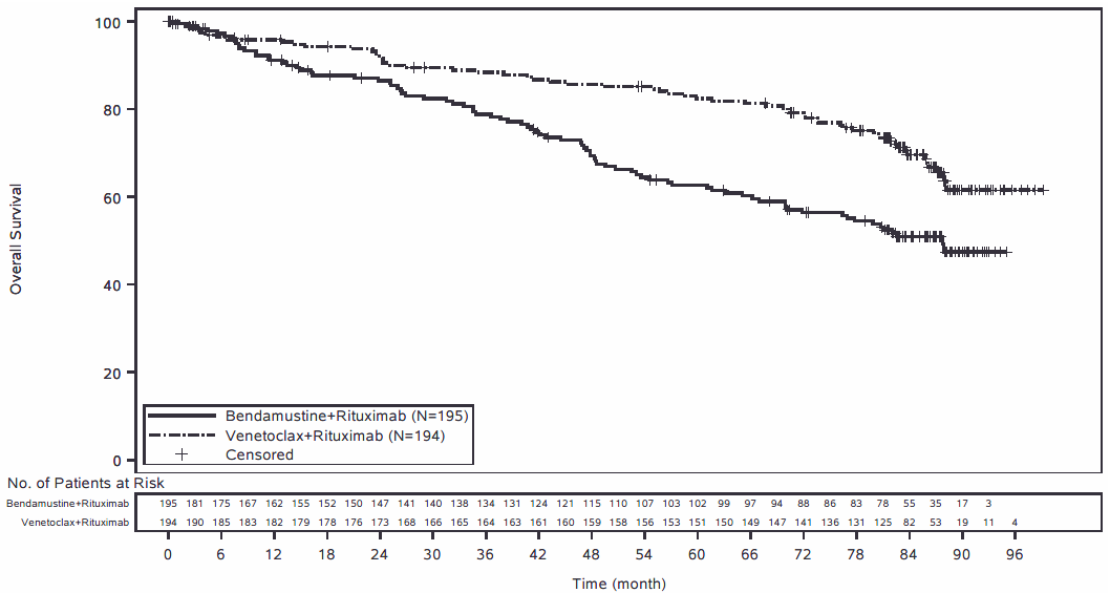



17p deletion status was determined based on central laboratory test results.
Unstratified hazard ratio is displayed on the X-axis with logarithmic scale.
NE=not evaluable.

*Final overall survival analysis (86-month follow-up)*

At the time of the final OS analysis (data cut-off date 03 August 2022), a total of 144 randomised patients had died; 60/194 patients (31%) in the venetoclax + rituximab arm and 84/195 patients (43%) in the bendamustine + rituximab arm. The median OS was not reached in the venetoclax + rituximab arm and was 88 months in the bendamustine + rituximab arm. The estimated risk of death was decreased by 47% for patients treated with venetoclax + rituximab (stratified HR = 0.53; 95% CI: 0.37, 0.74). The final OS analysis was not type I error controlled. The Kaplan-Meier curve of overall survival is shown in Figure 5.

Figure 5: Kaplan-Meier curve of overall survival (intent-to-treat population) in MURANO (data cut-off date 03 August 2022) with 86-month follow-up




*Venetoclax in combination with ibrutinib for the treatment of patients with previously untreated CLL – study CLL3011 (GLOW)*

GLOW was a randomized, open-label, phase 3 study of venetoclax in combination with ibrutinib versus chlorambucil in combination with obinutuzumab, conducted in patients with previously untreated active CLL who were 65 years or older, and adult patients <65 years of age with a CIRS score >6 or CrCL ≥30 to <70 mL/min, including 14 patients with clinical presentation of SLL. Patients with 17p deletion or known TP53 mutations were excluded. Patients (n = 211) were randomized 1:1 to receive either venetoclax in combination with ibrutinib or chlorambucil in combination with obinutuzumab.

Patients in the venetoclax plus ibrutinib arm received single agent ibrutinib for 3 cycles followed by venetoclax in combination with ibrutinib for 12 cycles (including 5-week venetoclax dose-titration). Each cycle was 28 days. Ibrutinib was administered at a dose of 420 mg daily. Venetoclax was administered according to the 5 week dose-titration, then at the recommended daily dose of 400 mg (see section 4.2 Posology and method of administration). Patients randomized to the chlorambucil plus obinutuzumab arm received treatment for 6 cycles. Obinutuzumab was administered at a dose of 1000 mg on Days 1 (or 100 mg on Day 1 and 900 mg on Day 2), 8 and 15 in Cycle 1. In

Cycles 2 to 6, 1000 mg obinutuzumab was given on Day 1. Chlorambucil was administered at a dose of 0.5 mg/kg body weight on Days 1 and 15 of Cycles 1 to 6. Patients with confirmed progression by IWCLL criteria after completion of either fixed-duration regimen could be treated with single-agent ibrutinib.

The median age was 71 years (range, 47 to 93 years), 58% were male, and 96% were white. All patients had a baseline ECOG performance status of 0 (35%), 1 (53%), or 2 (12%). At baseline, 18% of patients presented with 11q deletion and 52% with unmutated IGHV. The most common reasons for initiating CLL therapy included: constitutional symptoms (59%), progressive marrow failure (48%), lymphadenopathy (36%), splenomegaly (28%) and progressive lymphocytosis (19%). At baseline assessment for risk of tumor lysis syndrome, 25% of patients had high tumor burden. After 3 cycles of single-agent ibrutinib lead-in therapy, 2% of patients had high tumor burden. High tumour burden was defined as any lymph node $\geq$ 10 cm; or any lymph node $\geq$ 5 cm and absolute lymphocyte count $\geq 25 \times 10^9$/L.

Efficacy results for GLOW with a median follow-up time of 28 months are shown in Table 14, the Kaplan-Meier curve for PFS is shown in Figure 6, and rates of MRD negativity are shown in Table 15.

Table 14: Efficacy Results in Study CLL3011 (GLOW) in patients with previously untreated CLL

| **Endpoint**[a] | **venetoclax + ibrutinib N = 106** | **Chlorambucil + Obinutuzumab N = 105** |
|---|---|---|
| **Progression-free survival** | | |
| Number of events (%) | 22 (21) | 67 (64) |
| Median, months (95% CI) | NE (31.2, NE) | 21 (16.6, 24.7) |
| HR (95% CI) | 0.22 (0.13, 0.36) | |
| p-value[b] | <0.0001 | |
| **Complete response rate (%)**[c] | 39 | 11 |
| 95% CI | (29.4, 48.0) | (5.3, 17.5) |
| p-value[d] | <0.0001 | |
| **Overall response rate (%)**[e] | 87 | 85 |
| 95% CI | (80.3, 93.2) | (77.9, 91.6) |

CR = complete response; CRi = complete response with incomplete marrow recovery; HR = hazard ratio; IRC = Independent Review Committee; NE = not evaluable; nPR = nodular partial response; PR = partial response.

[a]Based on IRC assessment.

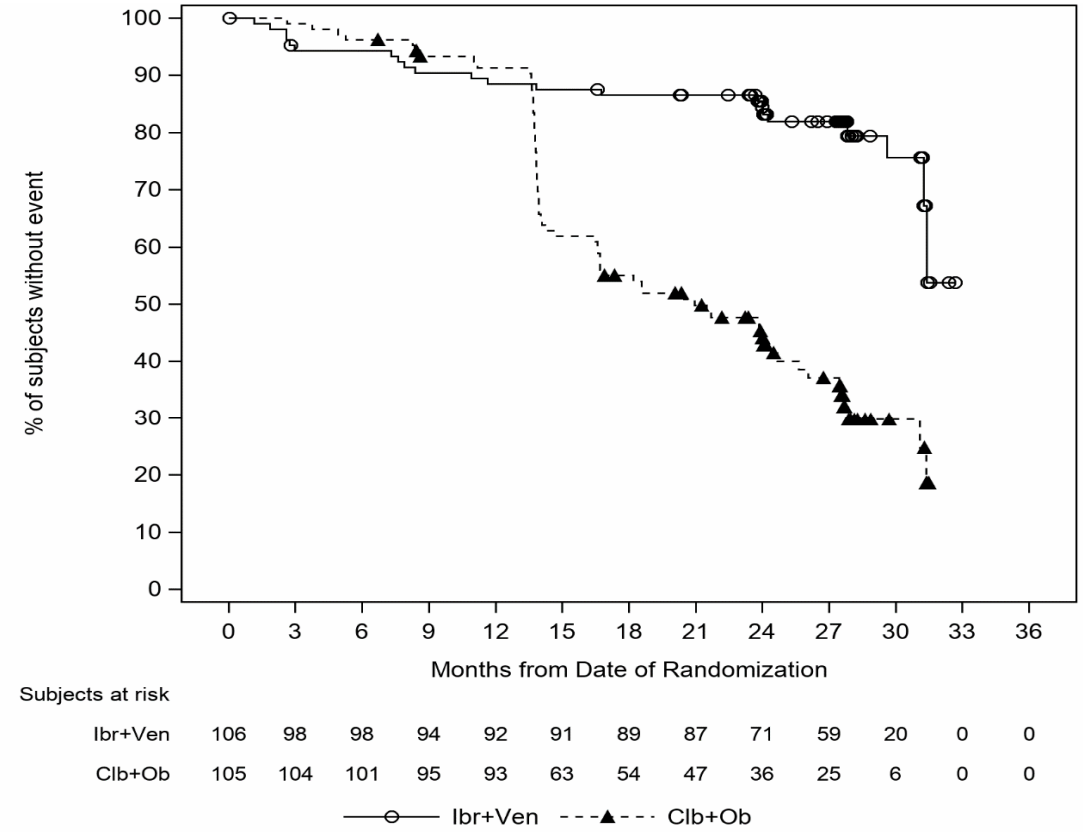
[b]Stratified log-rank test.

[c]Includes 3 patients in the venetoclax + ibrutinib arm with a complete response with incomplete marrow recovery (CRi).

[d]Cochran-Mantel-Haenszel chi-square test.

[e]Overall response = CR+CRi+nPR+PR.

Figure 6: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Patients with Previously Untreated CLL in Study CLL3011 (GLOW)




The PFS treatment effect of venetoclax plus ibrutinib versus chlorambucil plus obinutuzumab was consistent across predefined subgroups, including the high-risk population (TP53 mutation, 11q deletion, or unmutated IGHV), with a PFS HR of 0.23 [95% CI (0.13, 0.41)].
With a median follow-up of 28 months, overall survival data were not mature with a total of 23 deaths: 11 (10%) in the venetoclax plus ibrutinib arm and 12 (11%) in the chlorambucil plus obinutuzumab arm.

Table 15: Minimal Residual Disease Negativity Rates in Patients with Previously Untreated CLL in Study CLL3011 (GLOW)

| | **NGS Assay[a]** | | **Flow Cytometry[b]** | |
|---|---|---|---|---|
| | **venetoclax + ibrutinib N=106** | **Chlorambucil + Obinutuzumab N=105** | **venetoclax + ibrutinib N=106** | **Chlorambucil + Obinutuzumab N=105** |
| **MRD negativity rate** | | | | |
| Bone marrow, n (%) | 59 (56) | 22 (21) | 72 (68) | 24 (23) |
| 95% CI | (46.2, 65.1) | (13.2, 28.7) | (59.0, 76.8) | (14.8, 30.9) |
| p-value | <0.0001 | | <0.0001 | |
| Peripheral Blood, n (%) | 63 (59) | 42 (40) | 85 (80) | 49 (47) |
| 95 % CI | (50.1, 68.8) | (30.6, 49.4) | (72.6, 87.8) | (37.1, 56.2) |
| p-value | 0.0055 | | <0.0001 | |
| **MRD negativity rate at 3 months after completion of treatment** | | | | |

| | | | | |
|---|---|---|---|---|
| Bone marrow, n (%) | 55 (51.9) | 18 (17.1) | 60 (56.6) | 17 (16.2) |
| 95% CI | (42.4, 61.4) | (9.9, 24.4) | (47.2, 66.0) | (9.1, 23.3) |
| p-value | <0.0001 | | <0.0001 | |
| Peripheral Blood, n (%) | 58 (54.7) | 41 (39.0) | 65 (61.3) | 43 (41.0) |
| 95% CI | (45.2, 64.2) | (29.7, 48.4) | (52.0, 70.6) | (31.5, 50.4) |
| p-value | 0.0259 | | 0.0038 | |

CI = confidence interval; NGS = next-generation sequencing.
p-values are from Cochran-Mantel-Haenszel chi-square test. Except the p-value for MRD negativity rate in bone marrow by NGS, which is the primary MRD analysis and the first key secondary endpoint of GLOW, all other p-values are nominal.
All MRD results were derived from samples obtained from ≥80% of patients.
[a]Based on threshold of $10^{-4}$ using a next-generation sequencing assay (clonoSEQ).
[b]MRD was evaluated by flow cytometry of peripheral blood or bone marrow per central laboratory. The cut-off for a negative status was <1 CLL cell per $10^4$ leukocytes.

At three months after completion of treatment, 56 patients in the venetoclax plus ibrutinib arm who were MRD negative in peripheral blood by NGS assay had matched bone marrow specimens; of these, 52 patients (93%) were MRD negative in both peripheral blood and bone marrow.
Twelve months after the completion of treatment, MRD negativity rates in peripheral blood were 49% (52/106) by NGS assay and 55% (58/106) by flow cytometry in patients treated with venetoclax plus ibrutinib and, at the corresponding time point, was 12% (13/105) by NGS assay and 16% (17/105) by flow cytometry in patients treated with chlorambucil plus obinutuzumab.
TLS was reported in 6 patients treated with chlorambucil plus obinutuzumab and no TLS was reported in venetoclax in combination with ibrutinib.

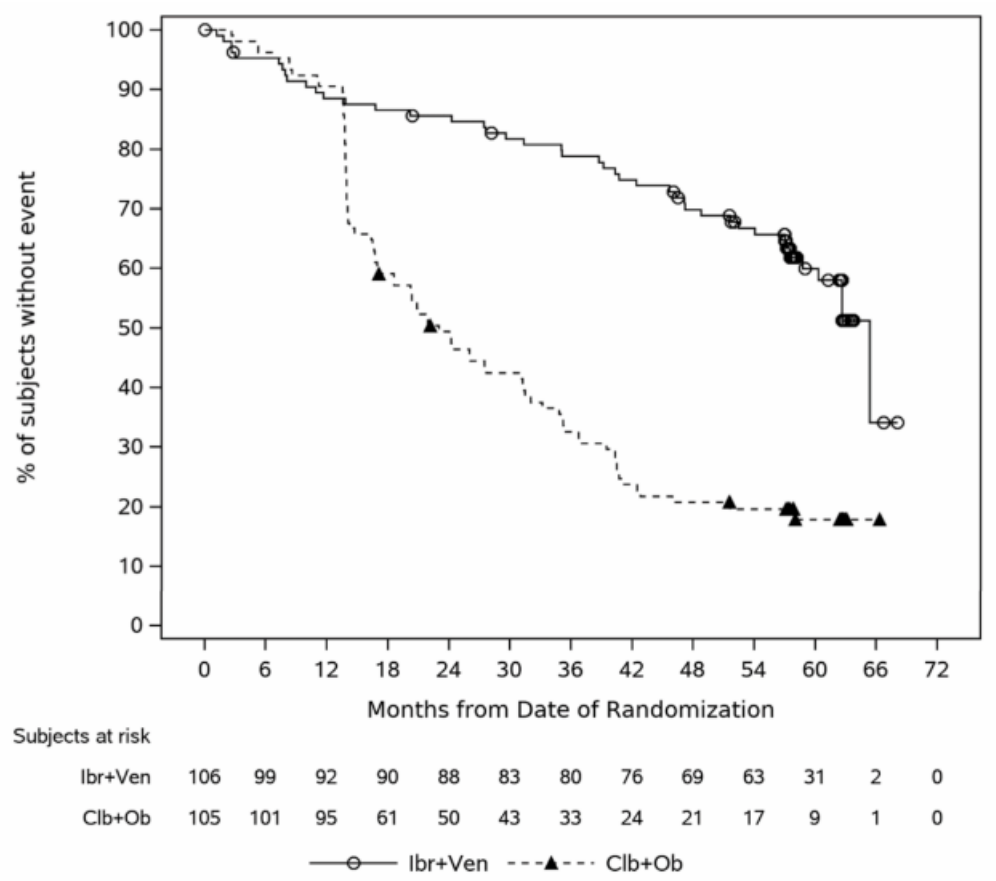
*64-month follow-up*
Efficacy was assessed with a median follow-up of 64.0 months (data cut-off date 24 February 2024). Efficacy results are presented in Table 16; the Kaplan-Meier curve for investigator-assessed PFS is shown in Figure 7.

Table 16. Efficacy Results of Study CLL3011 (GLOW) in Patients with Previously Untreated CLL (64-month Follow-Up).

| **Endpoint[a]** | **Venetoclax + Ibrutinib N = 106** | **Chlorambucil + Obinutuzumab N = 105** |
|---|---|---|
| **Progression-free survival** | | |
| Number of events (%) | 43 (41) | 84 (80) |
| Median[b], months (95% CI) | 65 (58.7, NE) | 23 (16.9, 31.2) |
| HR (95% CI) | 0.27 (0.18, 0.39) | |

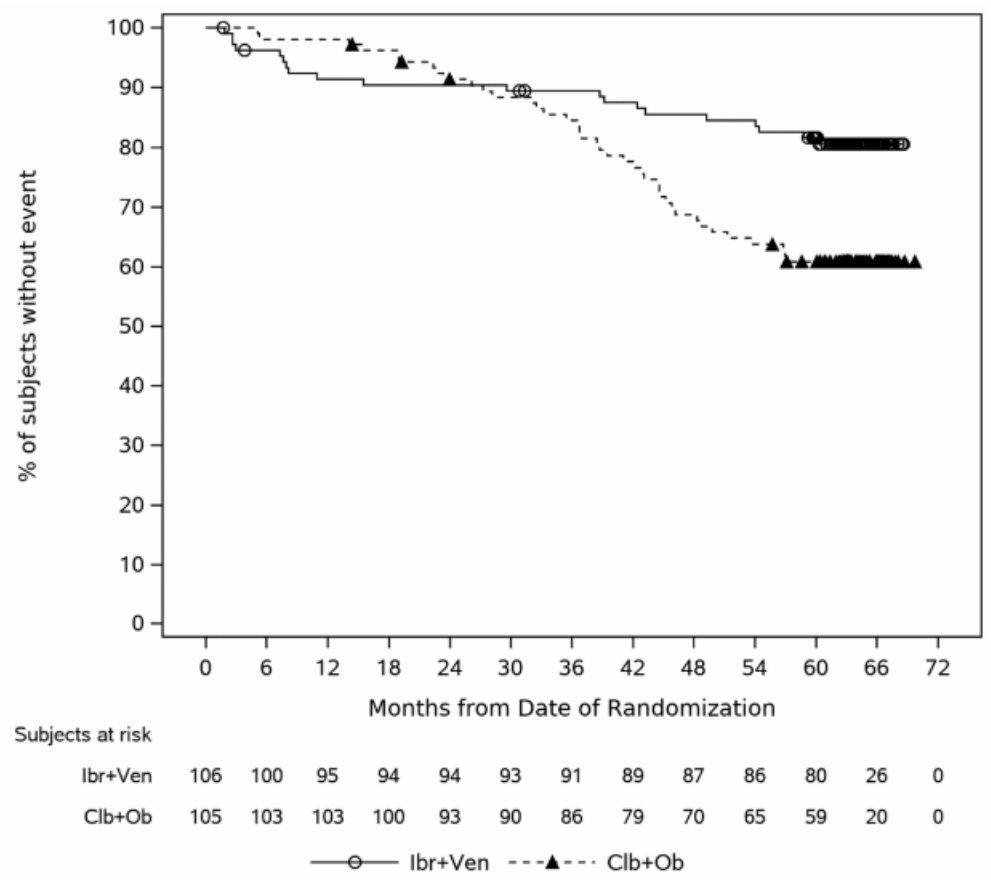
CI = confidence interval; HR = hazard ratio; NE = not evaluable.
[a]Based on investigator assessment.
[b]Median PFS for venetoclax + ibrutinib arm was not reliable as only 2 subjects were at risk at 66 months.

Figure 7. Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Patients with Previously Untreated CLL in Study CLL3011 (GLOW) (64-Month Follow-Up)




With a median follow-up of 64 months, 20 (19%) death events were observed in the venetoclax plus ibrutinib arm versus 40 (38%) death events in the chlorambucil plus obinutuzumab arm. Median OS was not reached in either arm. The Kaplan-Meier curve for OS is shown in Figure 8.

Figure 8. Kaplan-Meier Curve of Overall Survival (ITT Population) in Patients with Previously Untreated CLL in Study CLL3011 (GLOW) (64-Month Follow-Up)




*Venetoclax in combination with ibrutinib for the treatment of patients with previously untreated CLL – study PCYC-1142-CA (CAPTIVATE)*
CAPTIVATE was a phase 2, multicenter, 2-cohort study assessing both minimal residual disease (MRD)-guided discontinuation and fixed-duration (FD) therapy with venetoclax in combination with ibrutinib, conducted in adult patients who were 70 years or younger with previously untreated active CLL. The study enrolled 323 patients; of these, 159 patients were enrolled to FD therapy consisting of 3 cycles of single agent ibrutinib followed by venetoclax in combination with ibrutinib for 12 cycles (including 5-week dose-titration). Each cycle was 28 days. Ibrutinib was administered at a dose of 420 mg daily. Venetoclax was administered according to the 5-week dose-titration, then at the recommended daily dose of 400 mg (see section 4.2 Posology and method of administration).
Patients with confirmed progression by IWCLL criteria after completion of the FD regimen could be retreated with single-agent ibrutinib.
In the FD cohort the median age was 60 years (range, 33 to 71 years), 67% were male, and 92% were white. All patients had a baseline ECOG performance status of 0 (69%) or 1 (31%). The trial enrolled 146 patients with CLL and 13 patients with SLL. At baseline, 13% of patients presented with 17p deletion, 18% with 11q deletion, 17% with 17p deletion or TP53 mutation, 56% with unmutated IGHV and 19% with complex karyotype. The most common reasons for initiating CLL therapy included: lymphadenopathy (65%), progressive lymphocytosis (51%), splenomegaly (30%), fatigue (24%), progressive marrow failure demonstrated by anemia and/or thrombocytopenia (23%), and night sweats (21%). At baseline assessment for risk of tumor lysis

syndrome, 21% of patients had high tumor burden. After 3 cycles of single-agent ibrutinib lead-in therapy, 1% of patients had high tumor burden. High tumour burden was defined as any lymph node ≥ 10 cm, or any lymph node ≥ 5 cm and absolute lymphocyte count ≥25x$10^9$/L.

Efficacy results for CAPTIVATE with a median follow-up time of 28 months are shown in Table 17, and rates of minimal residual disease (MRD) negativity are shown in Table 18.

Table 17. Efficacy Results in study PCYC-1142-CA (CAPTIVATE); Fixed-Duration Cohort[a] in Patients with Previously Untreated CLL

| **Endpoint[a]** | **Venetoclax + Ibrutinib** | |
|---|---|---|
| | **Without Del 17p (N=136)** | **All (N=159)** |
| **Overall response rate, n (%)[b]** | 130 (96) | 153 (96) |
| 95% CI (%) | (92.1, 99.0) | (93.3, 99.2) |
| **Complete response rate, (%)[c]** | 61 | 60 |
| 95% CI (%) | (52.8, 69.2) | (52.1, 67.4) |
| Median duration of CR, months (range)[d] | NE (0.03+, 24.9+) | NE (0.03+, 24.9+) |

CR = complete response; CRi = complete response with incomplete marrow recovery; nPR = nodular partial response; PR = partial response; NE = not evaluable.

[a]Based on IRC assessment.

[b]Overall response = CR + CRi + nPR + PR.

[c]Includes 3 patients with a complete response with incomplete marrow recovery (CRi).

[d]A '+' sign indicates a censored observation.

Table 18. Minimal Residual Disease Negativity Rates in Patients with Previously Untreated CLL in study PCYC-1142-CA (CAPTIVATE); Fixed-Duration Cohort

| **Endpoint** | **Venetoclax + Ibrutinib** | |
|---|---|---|
| | **Without Del 17p (N = 136)** | **All (N = 159)** |
| **MRD negativity rate** | | |
| Bone marrow, n (%) | 84 (62) | 95 (60) |
| 95% CI | (53.6, 69.9) | (52.1, 67.4) |
| Peripheral Blood, n (%) | 104 (77) | 122 (77) |
| 95% CI | (69.3, 83.6) | (70.2, 83.3) |
| **MRD negativity rate at 3 months after completion of treatment** | | |
| Bone marrow, n (%) | 74 (54.4) | 83 (52.2) |
| 95% CI | (46.0, 62.8) | (44.4, 60.0) |
| Peripheral Blood, n (%) | 78 (57.4) | 90 (56.6) |
| 95% CI | (49.0, 65.7) | (48.9, 64.3) |

CI = confidence interval.

| Endpoint | Venetoclax + Ibrutinib | |
|---|---|---|
| | **Without Del 17p (N = 136)** | **All (N = 159)** |
| MRD was evaluated by flow cytometry of peripheral blood or bone marrow per central laboratory. The cut-off for a negative status was <1 CLL cell per $10^4$ leukocytes.<br>All MRD results were derived from samples obtained from ≥80% of patients. | | |

At this assessment, 84 patients who were MRD negative in peripheral blood had matched bone marrow specimens; of these, 76 patients (90%) were MRD negative in both peripheral blood and bone marrow.
In the fixed-duration cohort, no TLS was reported in patients treated with venetoclax in combination with ibrutinib.

*CLL/SLL with del 17p/TP53 in study PCYC-1142-CA (CAPTIVATE)*
In patients with del 17p/TP53 mutation (n = 27) the overall response rate based on IRC assessment was 96.3%; complete response rate was 55.6% and the median duration of complete response was not reached (range, 4.3 to 22.6 months). The MRD negativity rate in patients with del 17p/TP53 mutation 3 months after completion of treatment in bone marrow and peripheral blood was 40.7% and 59.3%, respectively.

*Venetoclax as monotherapy for the treatment of patients with CLL harbouring 17p deletion or TP53 mutation – study M13-982*
The safety and efficacy of venetoclax in 107 patients with previously treated CLL with 17p deletion were evaluated in a single-arm, open-label, multicentre study (M13-982). Patients followed a 4- to 5-week dose-titration schedule starting at 20 mg and increasing to 50 mg, 100 mg, 200 mg and finally 400 mg once daily. Patients continued to receive venetoclax 400 mg once daily until disease progression or unacceptable toxicity was observed. The median age was 67 years (range: 37 to 85 years); 65% were male, and 97% were white. The median time since diagnosis was 6.8 years (range: 0.1 to 32 years; N=106). The median number of prior anti-CLL treatments was 2 (range: 1 to 10 treatments); 49.5% with a prior nucleoside analogue, 38% with prior rituximab, and 94% with a prior alkylator (including 33% with prior bendamustine). At baseline, 53% of patients had one or more nodes ≥5 cm, and 51% had ALC ≥25 x $10^9$/l. Of the patients, 37% (34/91) were fludarabine refractory, 81% (30/37) harboured the unmutated *IgVH* gene, and 72% (60/83) had *TP53* mutation. The median time on treatment at the time of evaluation was 12 months (range: 0 to 22 months).

The primary efficacy endpoint was ORR as assessed by an IRC using the IWCLL updated NCI-WG guidelines (2008). Efficacy results are shown in Table 19. Efficacy data are presented for 107 patients with data cut-off date 30 April 2015. An additional 51 patients were enrolled in a safety expansion cohort. Investigator-assessed efficacy results are presented for 158 patients with a later data cut-off date 10 June 2016. The median time on treatment for 158 patients was 17 months (range: 0 to 34 months).

Table 19: Efficacy results in patients with previously treated CLL with 17p deletion (study M13-982)

| **Endpoint** | **IRC assessment (N=107)[a]** | **Investigator assessment (N=158)[b]** |
|---|---|---|
| Data cut-off date | 30 April 2015 | 10 June 2016 |
| ORR, %<br>(95% CI) | 79<br>(70.5, 86.6) | 77<br>(69.9, 83.5) |
| CR + CRi, % | 7 | 18 |
| nPR, % | 3 | 6 |
| PR, % | 69 | 53 |
| DOR, months, median (95% CI) | NR | 27.5 (26.5, NR) |
| PFS, % (95% CI)<br>12-month estimate<br>24-month estimate | <br>72 (61.8, 79.8)<br>NA | <br>77 (69.1, 82.6)<br>52 (43, 61) |
| PFS, months, median (95% CI) | NR | 27.2 (21.9, NR) |
| TTR, months, median (range) | 0.8 (0.1-8.1) | 1.0 (0.5-4.4) |

[a]One patient did not harbour the 17p deletion.
[b]Includes 51 additional patients from the safety expansion cohort.
CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery; DOR = duration of response; IRC = independent review committee; nPR = nodular PR; NA = not available; NR = not reached; ORR = overall response rate; PFS = progression-free survival, PR = partial remission; TTR = time to first response.

Minimal residual disease (MRD) was evaluated using flow cytometry in 93 of 158 patients who achieved CR, CRi, or PR with limited remaining disease with venetoclax treatment. MRD negativity was defined as a result below 0.0001 (<1 CLL cell per $10^4$ leukocytes in the sample). Twenty-seven percent (42/158) of patients were MRD negative in the peripheral blood, including 16 patients who were also MRD negative in the bone marrow.

*Venetoclax as monotherapy for the treatment of patients with CLL who have failed a B-cell receptor pathway inhibitor – study M14-032*
The efficacy and safety of venetoclax in patients with CLL who had been previously treated with and failed ibrutinib or idelalisib therapy were evaluated in an open-label, multicentre, non-randomised, phase 2 study (M14-032). Patients received venetoclax via a recommended dose-titration schedule. Patients continued to receive venetoclax 400 mg once daily until disease progression or unacceptable toxicity was observed.

At the time of data cut-off (26 July 2017), 127 patients were enrolled and treated with venetoclax. Of these, 91 patients had received prior ibrutinib therapy (Arm A) and 36 had received prior idelalisib therapy (Arm B). The median age was 66 years (range: 28 to 85 years), 70% were male, and 92% were white. The median time since diagnosis was 8.3 years (range: 0.3 to 18.5 years; N=96). Chromosomal aberrations were 11q deletion (34%,

43/127), 17p deletion (40%, 50/126), *TP53* mutation (38%, 26/68) and unmutated *IgVH* (78%, 72/92). At baseline, 41% of patients had one or more nodes ≥5 cm and 31% had ALC ≥25 x $10^9$/l. The median number of prior oncology treatments was 4 (range: 1 to 15) in ibrutinib-treated patients and 3 (range: 1 to 11) in idelalisib-treated patients. Overall, 65% of patients received prior nucleoside analogue, 86% rituximab, 39% other monoclonal antibodies, and 72% alkylating agent (including 41% with bendamustine). At the time of evaluation, median duration of treatment with venetoclax was 14.3 months (range: 0.1 to 31.4 months).

The primary efficacy endpoint was ORR according to IWCLL updated NCI-WG guidelines. Response assessments were performed at 8 weeks, 24 weeks, and every 12 weeks thereafter.

Table 20: Efficacy results as assessed by investigator in patients who have failed a B-cell receptor pathway inhibitor (study M14-032)

| **Endpoint** | **Arm A (ibrutinib failures) (N=91)** | **Arm B (idelalisib failures) (N=36)** | **Total (N=127)** |
|---|---|---|---|
| ORR, %<br>(95% CI) | 65<br>(54.1, 74.6) | 67<br>(49.0, 81.4) | 65<br>(56.4, 73.6) |
| CR + CRi, % | 10 | 11 | 10 |
| nPR, % | 3 | 0 | 2 |
| PR, % | 52 | 56 | 53 |
| PFS, % (95% CI)<br>12-month estimate<br>24-month estimate | <br>75 (64.7, 83.2)<br>51 (36.3, 63.9) | <br>80 (63.1, 90.1)<br>61 (39.6, 77.4) | <br>77 (68.1, 83.4)<br>54 (41.8, 64.6) |
| PFS, months, median (95% CI) | 25 (19.2, NR) | NR (16.4, NR) | 25 (19.6, NR) |
| OS, % (95% CI)<br>12-month estimate | <br>91 (82.8, 95.4) | <br>94.2 (78.6, 98.5) | <br>92 (85.6, 95.6) |
| TTR, months, median (range) | 2.5 (1.6-14.9) | 2.5 (1.6-8.1) | 2.5 (1.6-14.9) |
| 17p deletion and/or *TP53* mutation status<br>ORR, % (95% CI) | | | |
| Yes | (n=28)<br>61 (45.4, 74.9) | (n=7)<br>58 (27.7, 84.8) | (n=35)<br>60 (46.6, 73.0) |
| No | (n=31)<br>69 (53.4, 81.8) | (n=17)<br>71 (48.9, 87.4) | (n=48)<br>70 (57.3, 80.1) |
| CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery, nPR = nodular PR; NR = not reached, ORR = overall response rate. OS = overall survival; PFS = progression-free survival, PR = partial remission, TTR = time to first response. | | | |

The efficacy data were further evaluated by an IRC demonstrating a combined ORR of 70% (Arm A: 70%; Arm B: 69%). One patient (ibrutinib failure) achieved CRi. The ORR for patients with 17p deletion and/or *TP53* mutation was 72% (33/46) (95% CI: 56.5, 84.0) in Arm A and 67% (8/12) (95% CI: 34.9, 90.1) in Arm B. For patients without 17p deletion and/or *TP53* mutation,

the ORR was 69% (31/45) (95% CI: 53.4, 81.8) in Arm A and 71% (17/24) (95% CI: 48.9, 87.4) in Arm B.

Median OS and DOR were not reached with median follow-up of approximately 14.3 months for Arm A and 14.7 months for Arm B.

Twenty-five percent (32/127) of patients were MRD negative in the peripheral blood, including 8 patients who were also MRD negative in bone marrow.

*Acute myeloid leukaemia*

Venetoclax was studied in adult patients who were ≥ 75 years of age, or who had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2–3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, creatinine clearance (CrCl) < 45 ml/min, or other comorbidity.

*Venetoclax in combination with azacitidine for the treatment of patients with newly diagnosed AML - study M15-656 (VIALE-A)*

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

Patients in VIALE-A completed the 3-day daily titration schedule to a final 400 mg once daily dose during the first 28-day cycle of treatment (see section 4.2) and received venetoclax 400 mg orally once daily thereafter in subsequent cycles. 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. Placebo orally once daily was administered on Day 1-28 plus azacitidine at 75 mg/m$^2$ on Day 1-7 of each 28-day cycle beginning on Cycle 1 Day 1. During the titration, patients received TLS prophylaxis and were hospitalised for monitoring. Once bone marrow assessment confirmed a remission, defined as less than 5% leukaemia blasts with grade 4 cytopenia following Cycle 1 treatment, venetoclax or placebo was interrupted up to 14 days or until ANC ≥500/microlitre and platelet count ≥50 × 10$^3$/ microlitre. For patients with resistant disease at the end of Cycle 1, a bone marrow assessment was performed after Cycle 2 or 3 and as clinically indicated. Azacitidine was resumed on the same day as venetoclax or placebo following interruption (see section 4.2). Azacitidine dose reduction was implemented in the clinical study for management of hematologic toxicity (see azacitidine Summary of Product Characteristics). 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. Baseline demographic and disease characteristics were similar between the venetoclax + azacitidine and placebo + azacitidine arms. Overall, the median age was 76 years (range:

49 to 91 years), 76% were white, 60% were males, and ECOG performance status at baseline was 0 or 1 for 55% of patients, 2 for 40% of patients, and 3 for 5% of patients. There were 75% of patients with *de novo* AML and 25% with secondary AML. At baseline, 29% of patients had bone marrow blast count <30%, 22% of patients had bone marrow blast count ≥30% to <50%, and 49% had ≥50%. Intermediate or poor cytogenetic risk was present in 63% and 37% patients, respectively. The following mutations were identified: *TP53* mutations in 21% (52/249), *IDH1* and/or *IDH2* mutation in 24% (89/372), 9% (34/372) with *IDH1*, 16% (58/372) with *IDH2*, 16% (51/314) with *FLT3*, and 18% (44/249) with *NPM1*.

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

Venetoclax + azacitidine demonstrated a 34% reduction in the risk of death compared with placebo + azacitidine (p <0.001). Results are shown in Table 21.

Table 21: Efficacy results in VIALE-A

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

CI = confidence interval; CR = (complete remission) was defined as absolute neutrophil count >1,000/microlitre, platelets >100,000/microlitre, 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.

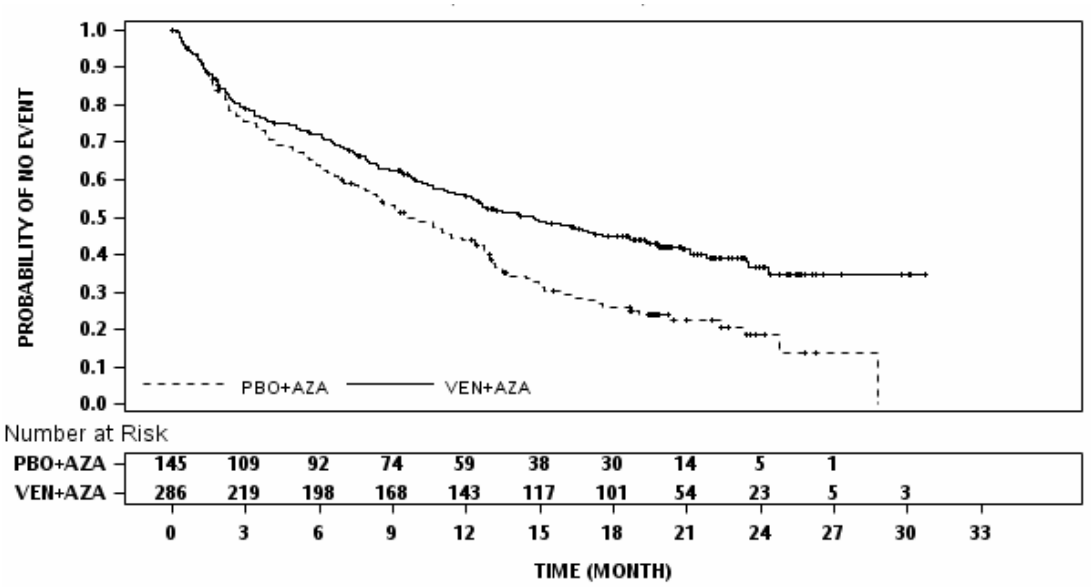
[a]Kaplan-Meier estimate at the second interim analysis (data cut-off date 4 January 2020).

[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 to <75, ≥75) as assigned at randomisation; p-value based on log-rank test stratified by the same factors.

[c]The CR+CRi rate is from a planned interim analysis of first 226 patients randomised

with 6 months of follow-up at the first interim analysis (data cut-off date 1 October 2018).
[d]P-value is from Cochran-Mantel-Haenszel test stratified by age (18 to <75, ≥75) and cytogenetic risk (intermediate risk, poor risk) as assigned at randomisation.

Figure 9: Kaplan-Meier curve for overall survival in VIALE-A




Key secondary efficacy endpoints are presented in Table 22.

Table 22: Additional efficacy endpoints in VIALE-A

| **Endpoint** | **Venetoclax + azacitidine N=286** | **Placebo + azacitidine N=145** |
|---|---|---|
| CR rate | | |
| n (%) | 105 (37) | 26 (18) |
| (95% CI) | (31, 43) | (12, 25) |
| p-value[a] | <0.001 | |
| Median DOR[b], months | 17.5 | 13.3 |
| (95% CI) | (15.3, -) | (8.5, 17.6) |
| CR+CRi rate | | |
| n (%) | 190 (66) | 41 (28) |
| (95% CI) | (61, 72) | (21, 36) |
| Median DOR[b], months | 17.5 | 13.4 |
| (95% CI) | (13.6, -) | (5.8, 15.5) |
| CR+CRi rate by initiation of Cycle 2, n (%) | 124 (43) | 11 (8) |
| (95% CI) | (38, 49) | (4, 13) |
| p-value[a] | <0.001 | |

| | | |
|---|---|---|
| Transfusion independence rate, platelets | | |
| n (%) | 196 (69) | 72 (50) |
| (95% CI) | (63, 74) | (41, 58) |
| p-value[a] | <0.001 | |
| Transfusion independence rate, red blood cells | | |
| n (%) | 171 (60) | 51 (35) |
| (95% CI) | (54, 66) | (27, 44) |
| p-value[a] | <0.001 | |
| CR+CRi MRD response rate[d] | | |
| n (% ) | 67 (23) | 11 (8) |
| (95% CI) | (19, 29) | (4, 13) |
| p-value[a] | <0.001 | |
| Event-free survival | 191 (67) | 122 (84) |
| Number of events, n (%) | 9.8 | 7.0 |
| Median EFS[e], months (95% CI) | (8.4, 11.8) | (5.6, 9.5) |
| Hazard ratio (95% CI)[c] | 0.63 (0.50, 0.80) | |
| p-value[c] | <0.001 | |

CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete blood count recovery; DOR = duration of response; EFS = event-free survival; MRD = minimal/measurable residual disease; n = number of responses or number of events; - = not reached.

CR (complete remission) was defined as absolute neutrophil count >1,000/microlitre, platelets >100,000/microlitre, red blood cell transfusion independence, and bone marrow with <5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.

Transfusion independence was defined as a period of at least consecutive 56 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.

[a]P-value is from Cochran-Mantel-Haenszel test stratified by age (18 to <75, ≥75) and cytogenetic risk (intermediate risk, poor risk) as assigned at randomisation.
[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, to the first date of confirmed morphologic relapse, confirmed progressive disease or death due to disease progression, whichever occurred earlier. Median DOR is from Kaplan-Meier estimate.
[c]Hazard ratio estimate (venetoclax + azacitidine vs. placebo + azacitidine) is based on Cox-proportional hazards model stratified by age (18 to <75, ≥75) and cytogenetics (intermediate risk, poor risk) as assigned at randomisation; p-value based on log-rank test stratified by the same factors.
[d] 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 standardized, central multicolour flow cytometry assay.
[e]Kaplan-Meier estimate.

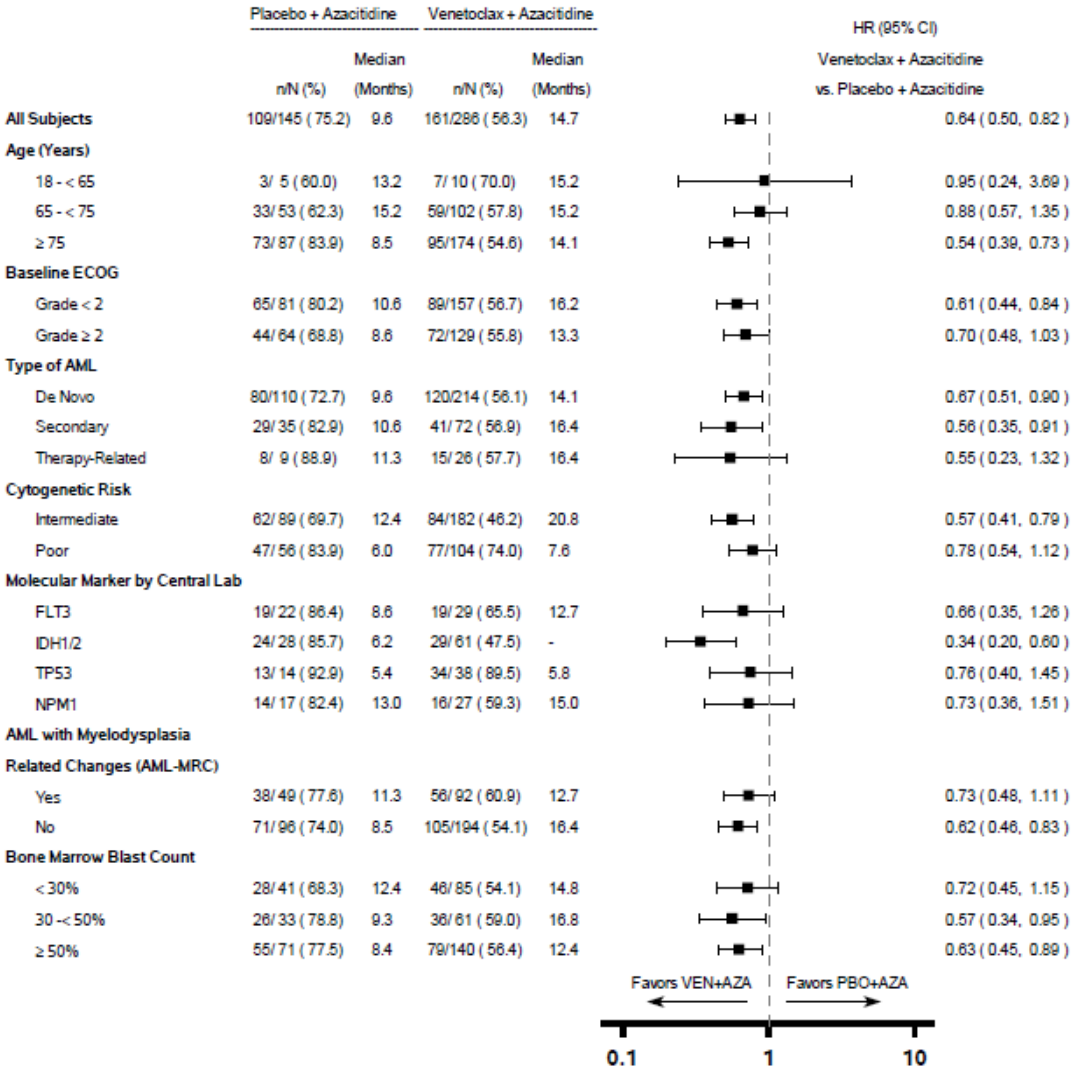
Of patients with the *FLT3* mutation, the CR+CRi rates were 72% (21/29; [95% CI: 53, 87]) and 36% (8/22; [95% CI: 17, 59]) in the venetoclax + azacitidine and placebo + azacitidine arms, respectively (p=0.021).

Of patients with *IDH1/IDH2* mutations, the CR+CRi rates were 75% (46/61; [95% CI: 63, 86]) and 11% (3/28; [95% CI: 2, 28]) in the venetoclax + azacitidine and placebo + azacitidine arms, respectively (p<0.001).

Of the patients who were RBC 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 months (range: 0.6 to 9.9 months) with venetoclax + azacitidine treatment. The median time to best response of CR or CRi was 2.3 months (range: 0.6 to 24.5 months).

Figure 10: Forest plot of overall survival by subgroups from VIALE-A



- = Not reached.
For the pre-specified secondary endpoint OS in the *IDH1/2* mutation subgroup, p<0.0001 (unstratified log-rank test).
Unstratified hazard ratio (HR) is displayed on the X-axis with logarithmic scale.

V*enetoclax in combination with azacitidine or decitabine for the treatment of patients with newly diagnosed AML - M14-358*
Study M14-358 was a non-randomised phase 1/2 clinical study of venetoclax in combination with azacitidine (n=84) or decitabine (n=31) in patients with newly diagnosed AML who were ineligible for intensive chemotherapy. Patients received venetoclax via a daily titration to a final 400 mg once daily dose. The administration of azacitidine in M14-358 was similar to that of VIALE-A randomised study. Decitabine at 20 mg/m$^2$ was administered intravenously on Days 1-5 of each 28-day cycle beginning on Cycle 1 Day 1.

The median follow-up was 40.4 months (range: 0.7 to 42.7 months) for venetoclax + decitabine.

The median age of patients treated with venetoclax + decitabine was 72 years (range: 65-86 years), 87% were white, 48% males, and 87% had ECOG score 0 or 1. The CR+CRi rate was 74% (95% CI: 55, 88) in combination with decitabine.

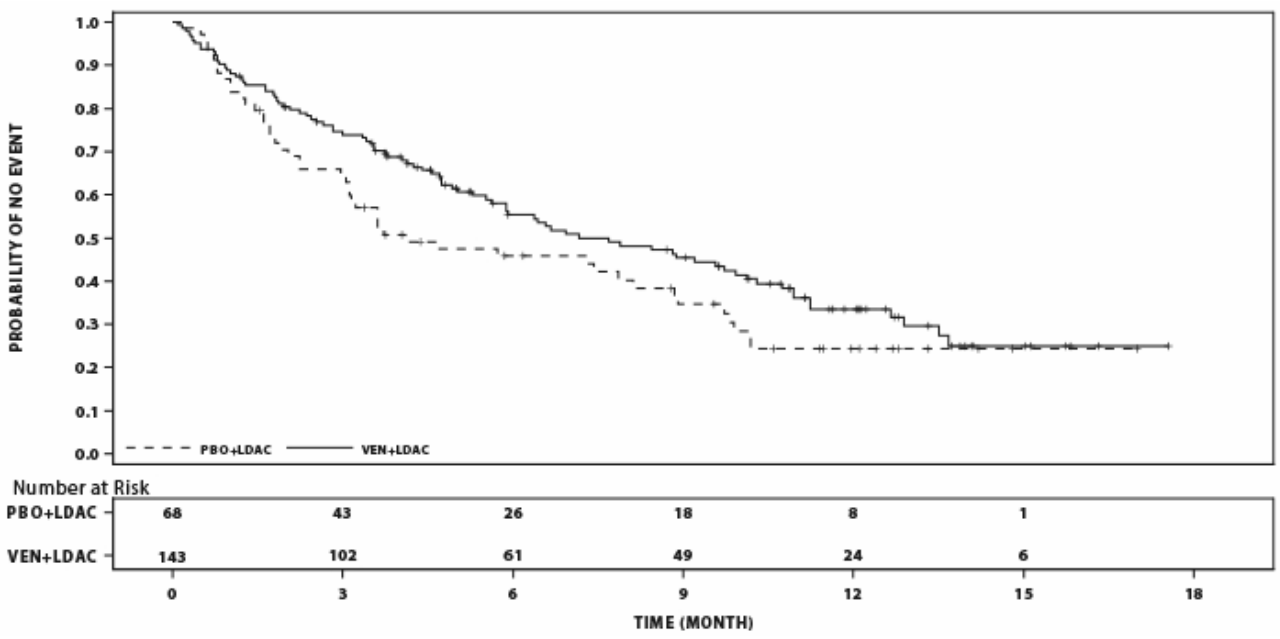
*Venetoclax in combination with low-dose cytarabine for the treatment of patients with newly-diagnosed AML study – M16-043 (VIALE-C)*
VIALE-C was a randomised (2:1), double-blind, placebo-controlled, multicentre, phase 3 study that evaluated the efficacy and safety of venetoclax in combination with low-dose cytarabine versus placebo combination with low-dose cytarabine in patients with newly-diagnosed AML who were ineligible for intensive chemotherapy.

Patients in VIALE-C completed the 4-day titration schedule to a final 600 mg once daily dose during the first 28-day cycle of treatment (see section 4.2) and received venetoclax 600 mg orally once daily thereafter in subsequent cycles. Low-dose cytarabine 20 mg/m$^2$ was administered subcutaneously (SC) once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1. Placebo orally once daily was administered on Days 1-28 plus low-dose cytarabine 20 mg/m$^2$ SC once daily on Days 1-10. During the titration, patients received TLS prophylaxis and were hospitalised for monitoring. Once bone marrow assessment confirmed a remission, defined as less than 5% leukaemia blasts with grade 4 cytopenia following Cycle 1 treatment, venetoclax or placebo was interrupted up to 14 days or until ANC $\geq$500/microlitre and platelet count $\geq 25 \times 10^3$/microlitre. For patients with resistant disease at the end of Cycle 1, a bone marrow assessment was performed after Cycle 2 or 3 and as clinically indicated. Low-dose cytarabine was resumed on the same day as venetoclax or placebo following interruption. 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.

A total of 211 patients were randomised: 143 to the venetoclax in combination with low-dose cytarabine arm and 68 to the placebo in combination with low-dose cytarabine arm. 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, 71% were white, and ECOG performance status at baseline was 0 or 1 for 51% of patients, 2 for 42%, and 3 for 7% 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 + 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.

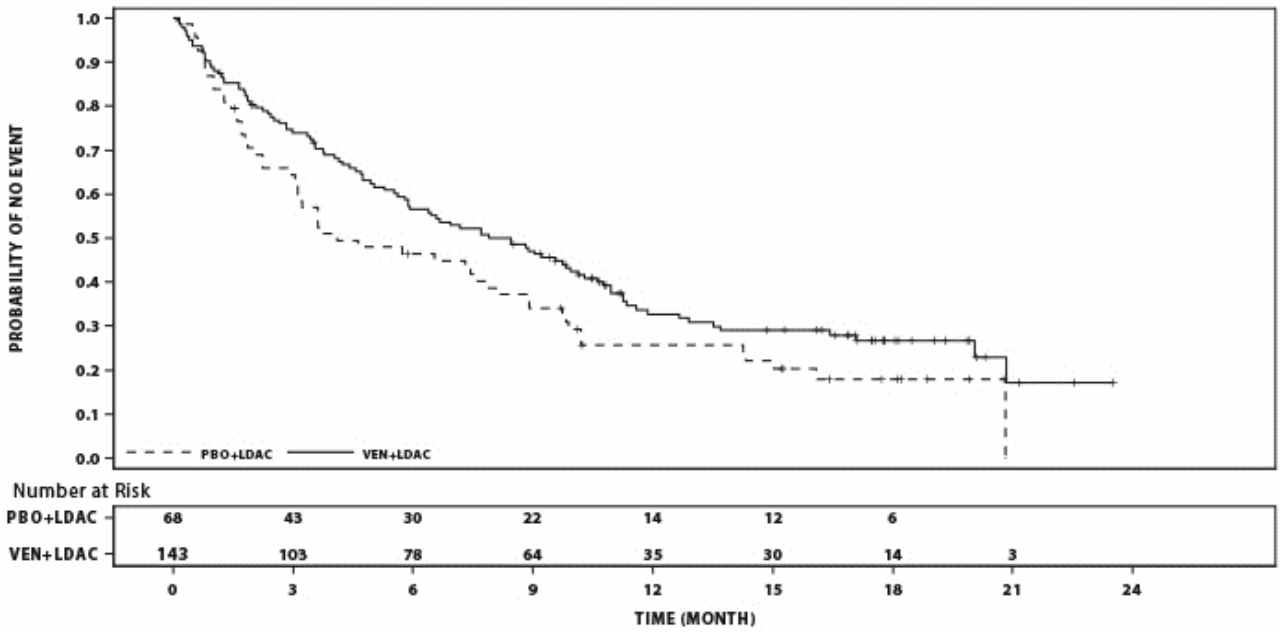
Figure 11: Kaplan-Meier curves of overall survival (primary analysis) in VIALE-C




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)

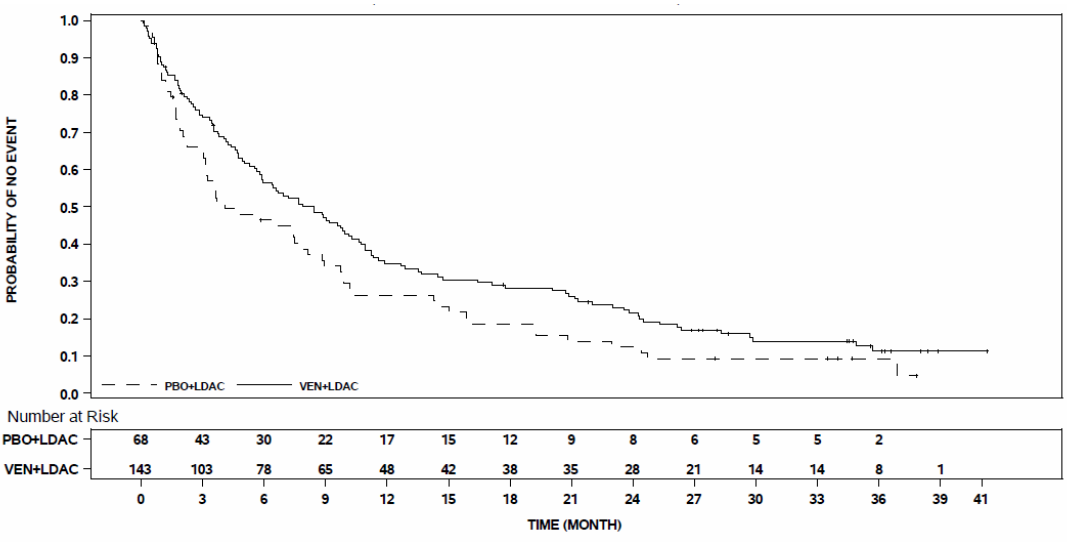
representing a 30% reduction in the risk of death for patients treated with venetoclax + low-dose cytarabine.

Figure 12: Kaplan-Meier curves of overall survival (6-month follow-up analysis) in VIALE-C




In the additional 24-month analysis for OS, the median OS in the venetoclax + low-dose cytarabine arm was 8.4 months (95% CI: 5.9, 10.3) and in the placebo + low-dose cytarabine arm was 4.1 months (95% CI: 3.1, 8.1). The hazard ratio was 0.71 (95% CI: 0.52, 0.98, nominal p= 0.036) representing a 29% reduction in the risk of death for patients treated with venetoclax + low-dose cytarabine.

Figure 13: Kaplan-Meier curves of overall survival (24-month follow-up analysis) in VIALE-C



Efficacy results for secondary endpoints from the primary analysis are shown in Table 23 below.

Table 23: Efficacy results for secondary endpoints from the primary analysis of VIALE-C

| **Endpoint** | **Venetoclax + low-dose cytarabine N=143** | **Placebo + low-dose cytarabine N=68** |
|---|---|---|
| CR, n (, %) | 39 (27) | 5 (7) |
| (95% CI) | (20, 35) | (2, 16) |
| Median DOR[a] (months) | 11.1 | 8.3 |
| (95% CI) | (5.9, -) | (3.1, 8.3) |
| CR+ CRi, n (%) | 68 (48) | 9 (13) |
| ( 95% CI) | (39, 56) | (6, 24) |
| Median DOR[a] (months) | 10.8 | 6.2 |
| (95% CI) | (5.9, -) | (1.1, -) |
| Transfusion independence rate[b], n (%) | 68 (48) | 22 (32) |
| Platelet (95% CI) | (39, 56) | (22, 45) |
| Red Blood Cell | 58 (41) | 12 (18) |
| (95% CI) | (32, 49) | (10, 29) |
| Event-free survival | | |
| Number of events, n (%) | 100 (70) | 54 (79) |
| Median EFS[c], months (95% CI) | 4.7 (3.7, 6.4) | 2.0 (1.6, 3.1) |
| Hazard ratio (95% CI)[d] | 0.61 (0.44, 0.84) | |

CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete blood count recovery; DOR = duration of response; n = number of responses; - = not reached.

[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, to the first date of confirmed morphologic relapse, progressive disease or death due to disease progression, whichever occurred earlier. Median DOR is from Kaplan-Meier estimate.
[b]Transfusion independence was defined as a period of at least consecutive 56 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 progressive or before the initiation of post treatment therapy whichever is earlier.
[c]Kaplan-Meier estimate.
[d]Hazard ratio estimate (venetoclax + low-dose cytarabine vs. placebo + low-dose cytarabine) is based on Cox-proportional hazards model stratified by age (18 to <75, ≥75) and AML status (de novo, secondary) as assigned at randomisation.

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 month (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 month (range: 0.8 to 5.9 months).

In the additional 24-months follow up analysis, CR+CRi rates for venetoclax + low-dose cytarabine was 48% (95% CI: 40, 57) and for placebo + low-dose cytarabine was 13% (95% CI: 6, 24), as per Investigator Assessment.

Minimal residual disease (MRD) 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) versus 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 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 SF 7a and improvement in GHS/QoL up to Cycle 9. Relative to placebo + low-dose cytarabine, patients receiving venetoclax + low-dose cytarabine observed reduction in PROMIS Cancer Fatigue SF 7a that achieved a minimum important difference (MID) between two arms of 3 points by Day 1 of Cycles 3 and 5 (-2.940 versus 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 a 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).

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 107 patients who were evaluated for efficacy from M13-982 study, 57% were 65 years or older.

Of the 127 patients who were evaluated for efficacy from M14-032 study, 58% were 65 years or older.

Of the 352 patients evaluated for safety from 3 open-label monotherapy studies, 57% were 65 years or older.

Of the 283 patients with newly diagnosed AML treated in the VIALE-A (venetoclax + azacitidine arm) clinical study, 96% were ≥65 years of age and 60% were ≥75 years of age.

Of the 31 patients treated with venetoclax in combination with decitabine in the M14-358 clinical study, 100% were ≥65 years of age and 26% were ≥75 years of age.

Of the 142 patients treated in the VIALE-C (venetoclax + low-dose cytarabine arm) clinical trial, 92% were ≥65 years of age and 57% were ≥75 years of age.

There were no clinically meaningful differences in safety or efficacy observed between older and younger patients in the combination and monotherapy studies.

Paediatric population

The safety, efficacy, and pharmacokinetics of venetoclax were evaluated in a two-part, multi-centre, open-label, phase 1 study (M13-833) of venetoclax as monotherapy or in combination with chemotherapy in 140 paediatric and young adult patients with relapsed or refractory malignancies. Patients received venetoclax, alone or in combination with chemotherapy, at an age- or weight-adjusted dose to match an adult equivalent target dose of 400 mg or 800 mg daily or intermittently (days 1-10) for 21-day cycles.

Part 1 enrolled 22 patients in a dose determination cohort (AML (n=10), acute lymphoblastic leukaemia [ALL] (n=5), neuroblastoma (n=3), and solid tumours (n=4)) and 18 patients in a dose escalation/de-escalation cohort (neuroblastoma (n=7) and solid tumours (n=11)).

Part 2 of the study enrolled 100 patients with the following: AML (n=27), ALL (n=26), non-Hodgkin lymphoma [NHL] (n=2), neuroblastoma (n=26), and an exploratory cohort of other tumours with BCL-2 expression or transcription factor 3-hepatic leukaemia factor ALL (n=19; solid tumours n=8 and other tumours n=11). Overall, across Part 1 and 2, the median age of patients was 6 years (range: 0-17 years) for patients with AML, 9 years (range: 0-25 years) for patients with ALL, 12 years (range: 3-21 years) for patients with NHL, 8 years (range: 1-17 years) for patients with neuroblastoma, 16 years (range: 3-24 years) for patients with solid tumours, and 10 years (range: 5-19 years) for patients with other tumours.

Efficacy analyses included patients from Part 1 and Part 2 (n=129), and excluded patients from the exploratory other tumours cohort. The ORR was 24% and the CR rate was 16% in the AML cohort, with an estimated median DOR of 2.6 months (95% CI: 0.5, 7.9). The ORR was 42% (all CR) in the ALL cohort, with an estimated median DOR of 10.2 months (95% CI: 2.8, 14.2). One of the two patients in the NHL cohort achieved a partial response; the DOR was 1.4 months. Median DOR was not estimable, and meaningful conclusions are limited due to the small sample size. The ORR was 31% and the CR rate was 22% in the neuroblastoma cohort, with an estimated median DOR of 9.3 months (95% CI: 3.9, NE). The ORR was 22% and the CR rate

was 4% in the solid tumours cohort, with an estimated median DOR of 11.1 months (95% CI: 3.1, NE).

The European Medicines Agency has deferred the obligation to submit the results of studies with Venclyxto in one or more subsets of the paediatric population in the treatment of malignant neoplasms of the haematopoietic and lymphoid tissue (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Absorption

Following multiple oral administrations, maximum plasma concentration of venetoclax was reached 5-8 hours after dose. 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 mcg/ml and $AUC_{24}$ was 32.8 ± 16.9 mcg•h/ml at the 400 mg once daily dose, and 2.7 ± 1.6 mcg/ml and 45.6 ± 30.6 mcg•h/ml, respectively, at the 600 mg once daily dose.

*Effect of food*

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. It is recommended that venetoclax should be administered with a meal (see section 4.2).

Distribution

Venetoclax is highly bound to human plasma protein with unbound fraction in plasma <0.01 across a concentration range of 1-30 micromolar (0.87-26 mcg/ml). The mean blood-to-plasma ratio was 0.57. The population estimate for apparent volume of distribution ($Vd_{ss}$/F) of venetoclax ranged from 256-321 L in patients.

Biotransformation

*In vitro* studies demonstrated that venetoclax is predominantly metabolised by cytochrome P450 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 interaction studies*

*Co-administration with CYP and UGT substrates*

*In vitro* studies indicated that venetoclax is not an inhibitor or inducer of CYP1A2, CYP2B6, CYP2C19, CYP2D6, or CYP3A4 at clinically relevant concentrations. Venetoclax is a weak inhibitor of CYP2C8, CYP2C9 and UGT1A1 *in vitro*, but it is not predicted to cause clinically relevant inhibition. Venetoclax is not an inhibitor of UGT1A4, UGT1A6, UGT1A9 and UGT2B7.

*Co-administration with transporter substrates/inhibitors*

Venetoclax is a P-gp and BCRP substrate as well as a P-gp and BCRP inhibitor and a weak OATP1B1 inhibitor *in vitro* (see section 4.5). 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 phase elimination half-life of venetoclax was approximately 26 hours. Venetoclax shows minimal accumulation with accumulation ratio of 1.30-1.44. 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 do not change over time.

Special populations

*Paediatric population*

Based on pharmacokinetic analysis in paediatric patients with relapsed/refractory malignancies, the use of weight-based dosing for patients 2 years and above would yield venetoclax plasma exposures that are comparable across different paediatric weight subgroups and comparable to those observed in adult patients receiving venetoclax 400 mg as shown in Table 24.

Table 24: Venetoclax exposures for paediatric weight groups in patients 2 years and above at 400 mg adult-equivalent dose

| **Paediatric Subgroup (n)** | **10 - ≤ 20 kg (5)** | **20 - ≤ 30 kg (4)** | **30 - ≤ 45 kg (6)** | **≥ 45 kg (13)** | **Adults** |
|---|---|---|---|---|---|
| $AUC_{24}$* (mcg•h/mL) | 22.4 ± 13.1 | 27.5 ± 27.5 | 38.3 ± 36.9 | 26.0 ± 24.3 | 32.8 ± 16.9 |

*Mean ± standard deviation

*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), 5 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 have been studied in 6 patients with ESRD requiring dialysis. Following a single dose of 100 mg venetoclax, unbound venetoclax $C_{max}$ and AUC in subjects with ESRD on a non-dialysis day were comparable to subjects with normal renal function. The unbound venetoclax AUC and $C_{max}$ on a dialysis day were approximately 1.8 to 1.9-fold of the exposures on a non-dialysis day, however, the range of individual total and unbound venetoclax exposures on a dialysis day was generally comparable to the corresponding range in subjects with normal renal function. Additionally, during dialysis, plasma venetoclax concentrations were

comparable between arterial and venous samples indicating that dialysis has no impact on the clearance of venetoclax (see section 4.2).

*Hepatic impairment*

Based on a population pharmacokinetic analysis that included 74 subjects with mild hepatic impairment, 7 subjects with moderate hepatic impairment and 442 subjects with normal hepatic function, venetoclax exposures are similar in subjects with mild and moderate hepatic impairment and normal hepatic function. 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; n=6) or moderate (Child-Pugh B; n=6) hepatic impairment were similar to subjects with normal hepatic function, after receiving a 50 mg single dose of venetoclax. In subjects with severe (Child-Pugh C; n=5) hepatic impairment, the mean venetoclax $C_{max}$ was similar to subjects with normal hepatic function but venetoclax $AUC_{inf}$ was on average 2.7-fold higher (range: no change to 5-fold higher) than venetoclax $AUC_{inf}$ in the subjects with normal hepatic function (see section 4.2).

Effects of age, sex, weight and race

Based on population pharmacokinetic analyses, age, sex, and weight do not have an effect on venetoclax clearance. The exposure is 67% higher in Asian subjects as compared to non-Asian subjects. This difference is not considered clinically relevant.

## 5.3 Preclinical safety data

Toxicities observed in animal studies with venetoclax included dose-dependent reductions in lymphocytes and red blood cell mass. Both effects were reversible after cessation of dosing with venetoclax, with recovery of lymphocytes occurring 18 weeks post treatment. Both B- and T-cells were affected, but the most significant decreases occurred with B-cells.

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.

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.

Carcinogenicity/genotoxicity

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.

Venetoclax was not genotoxic in bacterial mutagenicity assay, *in vitro* chromosome aberration assay and *in vivo* mouse micronucleus assay. The M27 metabolite was negative for genotoxicity in the bacterial mutagenicity and chromosomal aberration assays.

Reproductive toxicity

No effects on fertility were observed in fertility and early embryonic development studies in male and female mice. Testicular toxicity (germ cell loss) was observed in general toxicity studies in dogs at exposures of 0.5 to 18 times the human AUC exposure at a dose of 400 mg. Reversibility of this finding has not been demonstrated.

In embryo-foetal development studies in mice, venetoclax was associated with increased post-implantation loss and decreased foetal body weight at exposures of 1.1 times the human AUC exposure at a dose of 400 mg. The major human metabolite M27 was associated with post-implantation loss and resorptions at exposures approximately 9-times the human M27-AUC exposure at a 400 mg dose of venetoclax. In rabbits, venetoclax produced maternal toxicity, but no foetal toxicity at exposures of 0.1 times the human AUC exposure at a 400 mg dose.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

*Tablet core*
Copovidone (K 28)
Colloidal anhydrous silica (E551)
Polysorbate 80 (E433)
Sodium stearyl fumarate
Anhydrous calcium hydrogen phosphate (E341 (ii))

*Film-coating*
Iron oxide yellow (E172)
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol 3350 (E1521)
Talc (E553b)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

### 6.5 Nature and contents of container

Venclyxto film-coated tablets are supplied in PVC/PE/PCTFE aluminium foil blisters containing either 1, 2 or 4 film-coated tablets.

The film-coated tablets are supplied in cartons containing either 7 (in blisters of 1 tablet) or 14 tablets (in blisters of 2 tablets); or a multipack containing 112 tablets (4 x 28 tablets (in blisters of 4 tablets)).
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

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

## 7 MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
UK

## 8 MARKETING AUTHORISATION NUMBER(S)

PLGB 41042/0036

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/03/2024

## 10 DATE OF REVISION OF THE TEXT

20/04/2026