Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Venetoclax

Proprietary Product Name: Venclexta

Sponsor: AbbVie Pty Ltd

Date of first round report: 30 May 2016
Date of second round report: 27 September 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of common abbreviations

Abbreviation	Meaning
AE	adverse event
AIHA	autoimmune hemolytic anaemia
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
aPTT	activated partial thromboplastin time
ASO-PCR	allele-specific oligonucleotide polymerase chain reaction
AST	aspartate aminotransferase
Bcl	B-cell lymphoma
BMI	body mass index
BR	bendamustine + rituximab
CD	cluster of differentiation
CI	confidence interval
CLL	chronic lymphocytic leukaemia
CTLS	clinical tumour lysis syndrome
CR	complete remission
CRi	complete remission with incomplete bone marrow recovery
CSR	clinical study report
CT	computed tomography
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DOR	duration of overall response

Abbreviation	Meaning
EC50	50% effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCCr	estimated creatinine clearance rate using Cockcroft-Gault formula
eCRF	electronic case report form
EFS	event-free survival
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	European Quality of Life 5 Dimensions-5 Levels Questionnaire
EQ VAS	European Quality of Life 5 Dimensions Visual Analogue Scale
ERIC	European Research Initiative in CLL
ESMO	European Society for Medical Oncology
FCR	fludarabine, cyclophosphamide, and rituximab
EU	European Union
FFPE	formalin-fixed, paraffin-embedded
FISH	fluorescence in situ hybridization
G-CSF	granulocyte-colony stimulating factor
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
IBM	ideal body mass
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee

Abbreviation	Meaning
IEC	Independent Ethics Committee
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IgVH	immunoglobulin variable region heavy chain
IHC	immunohistochemistry
IRC	Independent Review Committee
IRB	Institutional Review Board
ITP	idiopathic thrombocytopenic purpura
IUO/RUO	investigational use only/research use only
IV	intravenous
IWCLL	International Workshop for Chronic Lymphocytic Leukemia
IxRS	Interactive Response System
LDH	lactate dehydrogenase
LDi	longest diameter
LSI	locus-specific identifier
LTLS	laboratory tumour lysis syndrome
LVEF	left ventricular ejection fraction
MDASI	MD Anderson Symptom Inventory
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MRI	magnetic resonance imaging
MUGA	multigated acquisition scan
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-WG	National Cancer Institute Working Group

Abbreviation	Meaning
NHL	non-Hodgkin's lymphoma
nPR	nodular partial remission
NPT	non-protocol anti-lymphoma therapy
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PET	positron emission tomography
PFS	progression-free survival
PG	pharmacogenetic(s)
PK	pharmacokinetic(s)
PR	partial remission
PR-i	CR except for incomplete recovery of blood counts
PR-nod	nodular partial response
PT	prothrombin time
QA	quality assurance
QC	quality control
QD	once daily
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-CLL16	Quality of Life Questionnaire-Chronic Lymphocytic Leukemia 16
QoL	quality of life
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation

Abbreviation	Meaning
SLL	small lymphocytic lymphoma
SMQ	standardized MedDRA query
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TLS	tumour lysis syndrome
TTNT	time to next anti-CLL treatment
TTP	time to progression
ULN	upper limit of normal
USA	United States of America
WBC	white blood cell

1. Introduction

This is a full Category 1 application (Type A) submission to register the new biological entity venetoclax.

1.1. Drug class and therapeutic indication

Venetoclax is a potent, selective and orally bioavailable small-molecule inhibitor of Bcl-2 which is an anti-apoptotic protein. Overexpression of Bcl-2 has been demonstrated in various haematologic and solid tumour malignancies and has been implicated as a resistance factor for certain therapeutic agents. Venetoclax helps restore the process of apoptosis by binding directly to the Bcl-2 protein, displacing pro-apoptotic proteins like BIM, triggering mitochondrial outer membrane permeabilisation and the activation of caspases.

The proposed indication is '*Venclexta is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy; this includes patients with 17p deletion.*'

1.2. Dosage forms and strengths

The submission proposes registration of the following dosage forms and strengths:

- 10 mg film-coated tablets containing the following inactive ingredients: copovidone, silicon dioxide, polysorbate 80, sodium stearylfumarate, calcium hydrogen phosphate, iron oxide yellow, polyvinyl alcohol, macrogol 3350, talc - purified, and titanium dioxide.
- 50 mg film-coated tablets containing the following inactive ingredients: copovidone, silicon dioxide, polysorbate 80, sodium stearylfumarate, calcium hydrogen phosphate, iron oxide yellow, iron oxide red, iron oxide black, polyvinyl alcohol, talc - purified, macrogol 3350 and titanium dioxide.
- 100 mg film-coated tablets containing the following inactive ingredients: copovidone, silicon dioxide, polysorbate 80, sodium stearylfumarate, calcium hydrogen phosphate, iron oxide yellow, polyvinyl alcohol, macrogol 3350, talc - purified, and titanium dioxide.

1.3. Dosage and administration

The dosage and administration as set out in the proposed Product Information are:

- The starting dose of venetoclax is 20 mg once daily for 7 days. The venetoclax dose must be administered according to a weekly dose titration schedule to the recommended daily dose of 400 mg over a period of 5 weeks as shown in Table 1.
- The 5-week dose titration schedule is designed to gradually reduce tumour burden (debulking) and decrease the risk of TLS.
- Treatment should continue until disease progression or venetoclax is no longer tolerated by the patient.

Table 1. Dosing Schedule for Venetoclax Dose Titration Phase

Week	Venetoclax Daily Dose
1	20 mg
2	50 mg

Week	Venetoclax Daily Dose
3	100 mg
4	200 mg
5 and beyond	400 mg

1.3.1. Risk Assessment and Prophylaxis for Tumour Lysis Syndrome

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

The risk of TLS is a continuum based on multiple factors, including comorbidities. Patients with high tumour burden (for example, any lymph node with a diameter ≥ 5 cm or high absolute lymphocyte count [ALC ≥ 25 x 10^9/L]) are at greater risk of TLS when initiating venetoclax. Prior to initiating venetoclax, tumour burden assessments, including radiographic evaluation (for example, CT scan) must be performed for all patients. Blood chemistry (creatinine, uric acid, potassium, phosphorus, and calcium) should be assessed in all patients and preexisting abnormalities corrected.

The prophylaxis measures listed below should be followed. More intensive measures (including hospitalisation) should be employed as overall risk increases:

- Hydration: Adequate hydration must be ensured prior to initiating therapy with venetoclax and throughout the dose titration phase, especially the first day of each dose titration dose. Intravenous fluids should be administered as clinically indicated based on overall risk of TLS or for those who cannot maintain adequate oral hydration.
- Anti-hyperuricaemic agents: Uric acid reducing agents (for example, allopurinol) should be administered for patients with high uric acid levels or at risk of TLS. Start 2-3 days prior to initiation of venetoclax; consider continuing through the dose titration phase.

1.3.2. Laboratory Assessments

Pre-dose: For all patients, blood chemistries should be assessed prior to initiating venetoclax to evaluate kidney function and correct pre-existing abnormalities. Blood chemistries should be reassessed before starting each subsequent dose titration dose of venetoclax.

Post-dose: For patients at risk of TLS, blood chemistries should be monitored at 6-8 h and at 24 h after initiating venetoclax. Electrolyte abnormalities should be corrected promptly. The next dose should not be administered until 24-h blood chemistry results have been evaluated. The same monitoring schedule should be followed when starting each subsequent dose titration dose.

Hospitalisation: Based on physician assessment, some patients, especially those at greater risk of TLS, may require hospitalisation on the day of the first dose of venetoclax for more intensive prophylaxis and monitoring through the first 24 h. Hospitalisation should be considered for subsequent dose titration doses based on reassessment of risk.

1.3.3. Dose Modifications Based on Toxicities

Dosing interruption and/or dose reduction may be required. See Table 2 for dose modifications for haematologic and other toxicities related to venetoclax. For patients who have had a dosing interruption greater than 1 week during the first 5 weeks of dose titration phase or greater than 2 weeks when at the daily dose of 400 mg, the risk of TLS is to be reassessed to determine if re-initiation with a reduced dose is necessary (for example, all or some levels of the dose titration schedule).

Table 2. Recommended Dose Modifications for Toxicities

Event	Occurrence	Action
Tumour Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS		Withhold the next day's dose. If resolved within 24-48 h of last dose, resume at the same dose.
		For any blood chemistry changes requiring more than 48 h to resolve, resume at a reduced dose (see Table 3)
		For any events of clinical TLS, resume at a reduced dose following resolution (see Table 3)
Non-Haematologic Toxicities		
Non-Haematologic Toxicities	1st occurrence	Interrupt venetoclax. 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. Follow dose reduction guidelines in Table 3 when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the physician.
Haematologic Toxicities		
Grade 3 or 4 neutropenia with infection or fever; or Grade 4 haematologic toxicities (except lymphopenia)	1st occurrence	Interrupt venetoclax. 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. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines in Table 3 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.		

Table 3. Dose Modification for Toxicity During Venetoclax Treatment

Dose at Interruption, mg	Restart Dose, mg[a]
400	300

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

1.3.4. Dose Modifications for Use with CYP3A Inhibitors

Concomitant use of venetoclax with strong or moderate CYP3A inhibitors increases venetoclax exposure and may increase the risk for TLS at initiation and during dose titration phase. Concomitant use of venetoclax with strong CYP3A inhibitors at initiation and during dose titration phase is contraindicated.

Concomitant use of venetoclax with moderate CYP3A inhibitors should be avoided at initiation and during dose titration phase. Consider alternative treatments. If a moderate CYP3A inhibitor must be used, the initiation and dose titration doses of venetoclax should be reduced by at least 2-fold.

For patients who have completed the dose titration phase and are on a steady daily dose of venetoclax, the dose should be reduced by at least 2-fold when used concomitantly with moderate CYP3A inhibitors and by at least 4-fold when used concomitantly with strong CYP3A inhibitors. The venetoclax dose that was used prior to initiating the CYP3A inhibitor can be resumed 2 to 3 days after discontinuation of the inhibitor.

1.3.5. Special Populations

1.3.5.1. Use in Elderly

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

1.3.5.2. Use in Paediatrics

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

1.3.5.3. Renal impairment

No specific clinical trials have been conducted in subjects with renal impairment. After a single oral administration of 200 mg radiolabeled [^{14}C]-venetoclax to healthy subjects, less than 0.1% of radioactive venetoclax dose was detected in urine. No dose adjustment is needed for patients with mild or moderate renal impairment (CrCl ≥ 30 mL/min) based on the results of the population pharmacokinetic analysis.

Patients with reduced renal function (CrCl < 80 mL/min) may require more intensive prophylaxis and monitoring to reduce the risk of TLS when initiating treatment with venetoclax. A recommended dose has not been determined for patients with severe renal impairment (CrCl < 30 mL/min) or patients on dialysis.

Reduced renal function (creatinine clearance [CrCl] < 80 mL/min) further increases the risk of TLS. The risk may decrease as tumour burden decreases with Venclexta treatment.

1.3.5.4. Hepatic impairment

No specific clinical trials have been conducted in subjects with hepatic impairment. No dose adjustment is recommended in patients with mild or moderate hepatic impairment based

on results of the population pharmacokinetic analysis. A recommended dose has not been determined for patients with severe hepatic impairment.

1.3.5.5. Use in Pregnancy

Pregnancy Category C

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

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

1.3.5.6. Use in Lactation

It is not known whether venetoclax or its metabolites are excreted in human breast milk. Nursing women should be advised to discontinue breastfeeding during treatment with venetoclax.

1.4. Other proposed changes to the PI

Not applicable.

2. Clinical rationale

In Western countries leukaemia has a prevalence of approximately 1 in 50 and B cell chronic lymphocytic leukaemia (CLL), accounts for over 25% of all cases in ethnic Caucasian populations. The age-adjusted incidence rate in the US is 3.9 per 100 000 men and women per year and the age adjusted death rate is 1.5 per 100 000 men and women per year. CLL is a disease of older people with the median age of diagnosis 72 years of age. CLL can be divided into benign and progressive groups by sequencing the CLL IgVH gene and comparing with germline sequences. CLL cases with unmutated IgVH genes, or greater than 98% sequence homology with germline, have a median survival of 8 years and those with mutated genes, or less than 98% sequence homology with germline have a median survival of 25 years. Acquired chromosomal abnormalities are found in over 80% of CLL cases and are major independent predictors of disease progression and survival. Overall, patients with 17p deletions have the shortest median treatment-free interval (9 months).

There have been a number of advances in therapy for CLL over the past few decades. Treatment using single agent alkylating agents was recently superseded by a combination of alkylating agent and nucleoside therapy that in turn has been replaced by the current standard of care, a combination of nucleoside analogue, alkylating agent, and monoclonal antibody therapy (fludarabine, cyclophosphamide and rituximab). Consequently, complete response rates have improved markedly from 7% to 72%, and historical comparisons would suggest that this improved response rate has translated into improved survival. Furthermore, in the past 5 years, targeted drugs have fundamentally changed the management and outcomes of CLL.

The pro survival Bcl-2 proteins play a central role in lymphocyte and CLL biology, where they regulate clonal selection and survival. Employing structure-based design to identify small molecules that bind Bcl-2 like protein 1 (BCL-xL), investigators developed navitoclax, the first-generation high-affinity inhibitor of Bcl-2 family proteins. Navitoclax enhanced the effect of

death signals and killed cells in a mechanistically canonical manner. A Phase I study of navitoclax showed activity in 50% of patients with relapsed or refractory CLL, but inhibition of Bcl-xL, a regulator of platelet senescence, led to dose-limiting thrombocytopenia. To generate a more potent and selective Bcl-2 inhibitor, navitoclax was reverse engineered which led to the development of venetoclax, a potent inhibitor of Bcl-2 with 100 times less activity against Bcl-xL. Consistent with its binding characteristics, venetoclax showed markedly less thrombocytopenia but because of potent Bcl-2 inhibition, more neutropenia compared to navitoclax.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The clinical dossier documented a clinical development program of pharmacology, efficacy and safety.

The reviewer noted that there were no Phase III studies presented.

The submission contained the following clinical information:

- The indication being sought for this new drug application is supported primarily by interim efficacy results from one Phase II pivotal study (Study M13-982), one Phase I supportive study (Study M12-175), and 2 additional supportive studies (Studies M14-032 and M13-365):
    i. Study M13-982 is a Phase II, open-label, multicenter, study evaluating the efficacy of venetoclax in R/R or previously untreated subjects with CLL harbouring 17p del.
    ii. Study M12-175 is a Phase I, first-in-human, open-label, dose-escalating, multicenter study evaluating the safety and pharmacokinetic profile of venetoclax under a QD dosing schedule in subjects with R/R CLL/SLL.
    iii. Study M14-032 is a Phase II, open-label, nonrandomised, multicenter study evaluating the efficacy and safety of venetoclax in subjects with R/R CLL after failure of a BCR signalling pathway inhibitor (ibrutinib or idelalisib treatment).
    iv. Study M13-365 is a Phase Ib, open-label, dose-escalating, multicenter study evaluating the safety and tolerability of venetoclax in combination with rituximab in subjects with relapsed CLL/SLL.
- Safety data from the above studies in addition to the following combination (2 conducted by Genentech/Roche) and biopharmaceutical studies were included in the safety analysis (limited efficacy data are available for Studies GO28440 and GP28331 and thus, were not included in the efficacy analysis):
    i. Study M12-175 is a Phase I, open-label, 2-arm study to evaluate the safety and pharmacokinetic profiles, to determine the MTD and RPTD of venetoclax in subjects with R/R NHL (Arm B) and to examine the food effect in the dose escalation portion of the study.
    ii. Study GO28440 is a Phase Ib, open-label, nonrandomised, multicenter, dose-finding and safety study of venetoclax administered in combination with bendamustine/rituximab (BR) in subjects with R/R or previously untreated CLL.
    iii. Study GP28331 is a Phase Ib, open-label, nonrandomised, multicenter, dose-finding and safety study of venetoclax administered in combination with obinutuzumab in subjects with R/R or previously untreated CLL.

- Biopharmaceutic and clinical pharmacology studies included 5 studies in healthy adult female volunteers of non-childbearing potential (Study M14-253 and Study M15-101 evaluated bioavailability of the venetoclax tablets [including food effect in Study M15-101]; Study M13-363 evaluated mass balance of venetoclax; Study M14-497 evaluated the effect of rifampin on the pharmacokinetics of venetoclax; and Study M15-065 evaluated the pharmacokinetics of warfarin when co-administered with venetoclax) and one study (Study M13-364) in subjects with R/R NHL to evaluate effects of ketoconazole on the pharmacokinetics of venetoclax.

3.2. Paediatric data

Not applicable.

3.3. Good clinical practice

All of the studies at US sites were conducted under a United States Investigational New Drug Application (IND). All non-US sites complied with local regulations. All of the sites (US and non-US) were conducted in accordance with recognised international scientific and ethical standards, including but not limited to the International Conference on Harmonisation guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312), and the European Community Directive 2001/20/EC.

The protocol, consent form, study subject information sheets, and advertisement were submitted by each investigator to a duly constituted Institutional Review Board for review and approval before study initiation. All patients provided written informed consent after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

The 12 clinical studies contributing to the clinical pharmacology evaluation of venetoclax are listed in Table 4. Due to the testicular toxicities observed in male dogs, all healthy volunteer studies were carried out in females of non-child bearing potential.

Table 4. Clinical Studies Contributing to the Clinical Pharmacology Evaluation of Venetoclax

Protocol	Phase	Study Design	Study Status; Type of Report
M12-175	Phase I PK/safety/ tolerability. First-in-Human Study	Open-label, dose-escalation and food-effect study of venetoclax monotherapy in subjects with relapsed or refractory CLL/SLL and NHL	Ongoing; full interim for CLL/SLL, but only safety for NHL
M14-253	Phase I BA (Coated vs. uncoated tablets)	Open-label, randomised, 2-period crossover study of the bioavailability of venetoclax in healthy female subjects of non-	Complete; full

Protocol	Phase	Study Design	Study Status; Type of Report
		childbearing potential	
M15-101	Phase I BA (Food Effect and Manufacturing Site Change)	Open-label, randomised, complete 4-period crossover study of the bioavailability and food effect of venetoclax in healthy female subjects of non-childbearing potential	Complete; full
M13-363	Phase I PK/Mass balance (absorption, distribution, metabolism and excretion)	Open-label, ADME study in healthy female subjects of non-childbearing potential	Complete; full
M13-364	Phase I PK/DDI (Ketoconazole)	Open-label study to assess effect of ketoconazole on the pharmacokinetics of venetoclax in subjects with relapsed or refractory NHL	Complete; full
M14-497	Phase I PK/DDI (Rifampin)	Open-label study to assess the effect of rifampin on the pharmacokinetics of venetoclax in healthy female subjects of non-childbearing potential	Complete; full
Protocol	Phase	Study Design	Study Status; Type of Report
M15-065	Phase I PK/DDI (Warfarin)	Open-label study to assess the effect of venetoclax on the pharmacokinetics of warfarin in healthy female subjects of non-childbearing potential	Complete; full
M13-982	Phase II Efficacy/ safety	Open-label study of venetoclax in subjects with relapsed or refractory CLL harbouring 17p del	Ongoing; full interim
M14-032	Phase II Efficacy/ safety	Open-label, 2-arm study of venetoclax in subjects with CLL relapsed after or refractory to treatment with B-cell receptor signaling pathway inhibitors	Ongoing; abbreviated interim
M13-365	Phase Ib Safety/ tolerability of combination therapy (+ rituximab)	Open-label, dose-escalation study of venetoclax + rituximab in subjects with relapsed CLL and SLL	Ongoing; full interim
GP28331a	Phase Ib Safety/ tolerability of combination therapy (+ obinutuzumab)	Open-label, dose-finding and safety study of venetoclax in combination with obinutuzumab in subjects with relapsed, refractory or previously untreated CLL	Ongoing; full interim

Protocol	Phase	Study Design	Study Status; Type of Report
GO28440a	Phase Ib Safety/ tolerability of combination therapy (bendamustine + rituximab)	Open-label, dose-escalation study of venetoclax in combination with BR in subjects with relapsed, refractory or previously untreated CLL	Ongoing; full interim

BA = bioavailability

4.2. Summary of pharmacokinetics

4.2.1. Basic PK Properties of Venetoclax

4.2.1.1. Absorption

Following multiple-dose administration, the maximum plasma concentration of venetoclax was attained by 5 to 8 h. The harmonic mean terminal half-life ($t_{1/2}$) ranged from 17 to 41 h following a single oral dose of venetoclax, which supports the proposed daily dosing. Venetoclax was administered with food in all clinical studies, as food increased the bioavailability of venetoclax by approximately 3 to 5 fold.

In subjects with CLL/SLL, venetoclax plasma concentrations peaked at approximately 6 to 8 h after a single dose. At the 200 mg dose level (highest single dose administered in subjects with CLL), the mean C_{max} and AUC_{∞} were 1.15 µg/mL and 49.5 µg•h/mL, respectively (Study M12-175). Following multiple-dose administration of venetoclax, the median T_{max} ranged from 5 to 8 h, and the mean (± standard deviation) C_{max} and AUC_{0-24} were 2.1 ± 1.1 µg/mL and 32.8 ± 16.9 µg•h/mL, respectively, at the 400 mg dose level. In subjects with CLL, venetoclax steady-state AUC increased proportionally over the dose range of 150 to 800 mg.

4.2.1.2. Distribution

Venetoclax and M27 do not partition preferentially into the blood cellular compartment. The population estimate for apparent volume of distribution (Vdss/F) of venetoclax ranged from 256 to 321 L in subjects with CLL/SLL and NHL (Study M12-175).

4.2.1.3. Metabolism

M27 was identified as a major metabolite with an inhibitory activity against Bcl-2 that is at least 58-fold lower than venetoclax in vitro. Venetoclax and M27 are predominantly metabolised by cytochrome P450 (CYP) 3A4 (CYP3A4) in vitro; UDP-glucuronosyltransferases (UGTs) are not involved in the metabolism of venetoclax. Drug-drug interaction studies with ketoconazole, rifampin and warfarin were conducted to provide dosing recommendations for venetoclax in subjects who were concomitantly taking CYP3A inhibitors, CYP3A inducers or warfarin.

The mean plasma terminal elimination half-life of venetoclax was approximately 17 to 41 h in subjects with CLL/SLL (Study M12-175).

4.2.1.4. Excretion

Venetoclax is highly bound to plasma proteins with unbound fraction (fu) < 0.01, and it is primarily eliminated as metabolites in faeces with negligible renal elimination (< 0.1%). After a single oral administration of 200 mg radiolabeled [^{14}C]venetoclax in healthy subjects (Study M13-363), > 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 most significant metabolites in faeces were M30 and M34, which accounted for 12.9% and 16.9%, respectively, of the administered dose. Other minor

metabolites were detected in faeces: M2, M5, M14, M16, M17, M18, M23, M27, M31, M32, M33, M35, M36, M37, Unknown 3 and Unknown 4, each representing < 9% of the administered dose.

4.2.1.5. Drug-Drug Interaction Studies

The results from Studies M13-364, M14-497 and M12-175 and the population pharmacokinetic analyses, support in vitro studies that demonstrated venetoclax is predominately metabolized by CYP3A. Due to the lack of effect of weak CYP3A inhibitors and inducers on venetoclax CL/F, respectively, venetoclax dosage adjustments are not necessary when co-administered with these drug categories. Based on the magnitude of the 6.4-fold increase in venetoclax AUC with strong CYP3A inhibitors and in order not to expose patients to an increased risk for TLS and/or other possible adverse events, concomitant use of venetoclax with strong CYP3A inhibitors (for example, ketoconazole, ritonavir, clarithromycin, itraconazole, voriconazole) during the initiation and ramp-upphase is contraindicated. Moderate CYP3A inhibitors showed a smaller effect on venetoclax CL/F (16% decrease in the population pharmacokinetic analysis and 30 to 40% decrease in the non-compartmental analyses in Study M12-175) and concomitant use of moderate CYP3A inhibitors (for example, erythromycin, ciprofloxacin, diltiazem, fluconazole, verapamil) during the ramp-up phase with venetoclax is not recommended. If a moderate CYP3A inhibitor must be used, reducing the initiation and ramp-up doses of venetoclax by at least 2-fold should be considered. Grapefruit, Seville oranges, and star fruit contain CYP3A inhibitors and should also be avoided during treatment with venetoclax, especially at initiation and during ramp-up. For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax, venetoclax dose should be reduced by at least 2-fold when it is used concomitantly with moderate CYP3A inhibitors and should be reduced by at least 4-fold when used concomitantly with strong CYP3A inhibitors. The dose that was used prior to initiating the CYP3A inhibitor should be resumed 2 to 3 days after discontinuation of the inhibitor. These proposed dose reductions for moderate and strong CYP3A are based on the estimated effect on exposure and/or CL/F in the ketoconazole study, the population pharmacokinetic analysis, and the non-compartmental analyses in Study M12-175.

Based on the results of the rifampin study, concomitant use of venetoclax with strong CYP3A inducers (for example, carbamazepine, phenytoin, rifampin, St. John's Wort) or moderate CYP3A inducers (for example, bosentan, efavirenz, etravirine, modafinil, nafcillin) should be avoided. Alternative treatments with less CYP3A induction should be considered.

4.2.2. Summary of Results of Individual Studies

4.2.2.1. Study M14-253: A Phase I Open-Label Study Evaluating the Relative Oral Bioavailability of ABT-199 Phase III Formulation Against ABT-199 Phase I Formulation Under Fed Conditions in Healthy Female Subjects of Non-Childbearing Potential

Study Objectives and Design

The objectives of this study were to:

- Assess the oral bioavailability of ABT-199 Phase III tablet (50 mg, film-coated) relative to that of the Phase I tablet (50 mg, uncoated) under fed conditions in healthy female subjects of non-childbearing potential.
- Assess the safety of ABT-199 administered as single 50 mg doses in healthy female subjects of non-childbearing potential.

This Phase I, single-dose, open-label study was conducted according to a two-period, randomised, crossover design. Adult female subjects of non-childbearing potential in general good health were selected to participate in the study according to the selection criteria.

Having met the selection criteria, 15 subjects were randomly assigned to the two sequences of Regimens A and B as shown in Table 5.

Table 5. Sequence Groups

Regimens			
Sequence Group	Number of Subjects	Period 1	Period 2
I	7	A	B
II	8	B	A

Study drug was administered in the morning on Study Day 1 of each period as follows:

Regimen A: One ABT-199 50 mg tablet (Phase I Formulation, uncoated) administered under fed conditions (reference). Regimen B: One ABT-199 50 mg tablet (Phase III Formulation, film-coated) administered under fed conditions (test).

Each dose of study drug was taken orally with approximately 240 mL of water approximately 30 minutes after starting a standard breakfast. The sequence of regimens was such that each subject received both regimens prior to completion of the study. A washout interval of 7 days separated the doses of the two study periods. Subjects were confined to the study site and supervised for a minimum of 5 days in each study period. Confinement in each period began on Study Day –1 (1 day prior to the dosing day) and ended after the completion of all study procedures on Study Day 4. Serial blood samples were collected for 72 h after dosing in each period. Safety was assessed throughout the study.

Comment: The crossover design of this study is standard for comparing regimens since it provides within-subject comparisons and increases the power of the statistical analysis. A washout of at least 7 days between doses was sufficient to ensure no drug carryover since the half-life of ABT-199 is approximately 17 h.

Pharmacokinetic Results

Bioavailability

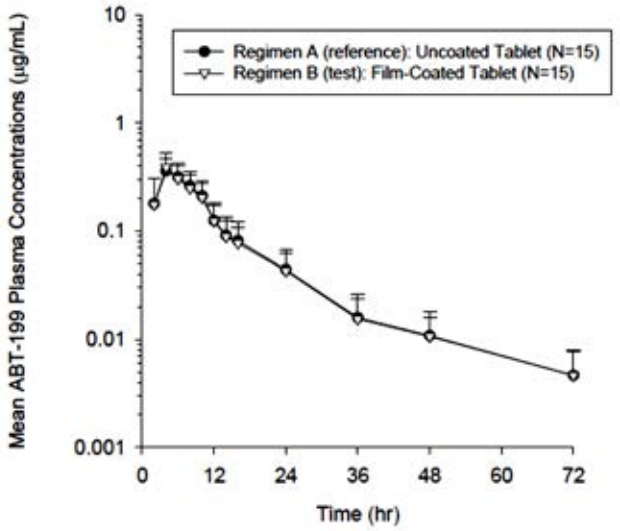
The bioavailability of a single oral dose of the venetoclax 50 mg Phase III film-coated tablet formulation relative to that of venetoclax 50 mg Phase I uncoated tablet formulation was evaluated. Each dose of study drug was taken orally approximately 30 minutes after starting a standard breakfast. The two formulations were bioequivalent because the 90% confidence intervals for C_{max} and AUC ratios were within 0.80 to 1.25 (Table 6). The mean and standard deviation (+SD) plasma concentration-time profiles are presented in Figure 1 on a log-linear scale.

Table 6. Relative Bioavailability and 90% Confidence Intervals for Venetoclax (Study M14-253)

Relative Bioavailability					
		Central Value			
Regimens Test vs. Reference	**Pharmacokinetic Parameter**	**Test**	**Refe-rence**	**Point Estimate**	**90% Confidence Interval**
B (film-coated)	C_{max}	0.387	0.373	1.037	0.962 – 1.117
versus	AUC_t	4.058	4.093	0.991	0.928 – 1.059

				Relative Bioavailability	
A (uncoated)	AUC_{∞}	4.186	4.216	0.993	0.930 – 1.060

Figure 1. Mean + Standard Deviation Concentration Time Profiles of 50 mg Venetoclax Tablets in Study M14-253



Conclusions

Under fed conditions, the test ABT-199 50 mg film-coated Phase III tablet formulation (Regimen B) met the bioequivalence criteria to the reference ABT-199 50 mg uncoated Phase I tablet formulation (Regimen A).

4.2.2.2. Study M15-101: A Phase I, Open-Label, Randomized, Crossover Study Evaluating Bioavailability and Food Effect of ABT-199 Tablets in Healthy Female Subjects of Non-Childbearing Potential

Study Objectives and Design

Primary Objective: The primary objectives of this study were to compare the relative bioavailability (BA) of 100 mg venetoclax film-coated tablets manufactured in Sligo, Ireland to that of 100 mg venetoclax film-coated tablets manufactured in USA under non-fasting (low-fat meal) conditions, and to assess the effect of food (low-fat meal or high-fat meal compared to fasting conditions) on the pharmacokinetics of venetoclax film-coated tablets manufactured in Ireland.

Secondary Objective: The secondary objective was to evaluate the safety and tolerability of venetoclax 100 mg film-coated tablet in healthy female subjects of non-childbearing potential.

This Phase I, single-dose, fed and fasting, open-label study was conducted according to a four-period, randomised, complete crossover design. Adult female subjects of non-childbearing potential (N = 24) in general good health were selected to participate in the study according to the protocol selection criteria. Subjects were randomly assigned in equal numbers to one of the four sequences of regimens shown in Table 7.

Table 7. Sequence Groups

Regimens					
Sequence Group	Subject Numbers	Period 1	Period 2	Period 3	Period 4
I	6	A	D	B	C
II	6	B	A	C	D
III	6	C	B	D	A
IV	6	D	C	A	B

The doses in each period were separated by at least a 7-day washout interval. A single dose of venetoclax was to be administered on Day 1 (Section 11.3) in each period as follows:

Regimen A One venetoclax 100 mg film-coated tablet (manufactured in Sligo, Ireland) administered under fasting conditions (after an approximate 10-h fast and at least 4 h prior to lunch).

Regimen B One venetoclax 100 mg film-coated tablet (manufactured in Sligo, Ireland) administered approximately 30 minutes after start of a low-fat (512 kcal, 25.1% of kcal from fat) breakfast.

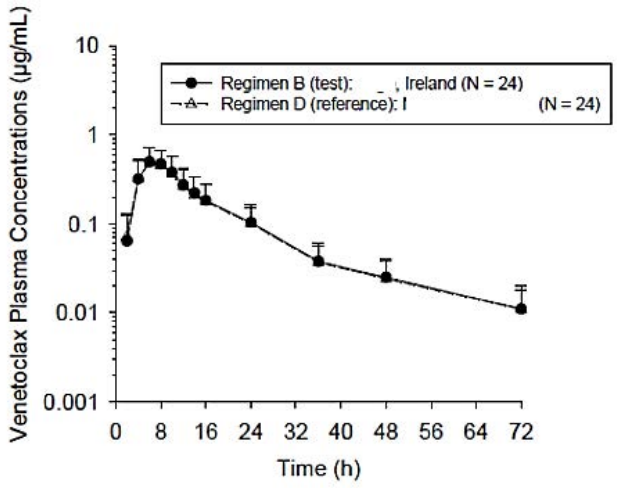
Regimen C One venetoclax 100 mg film-coated tablet (manufactured in Sligo, Ireland) administered approximately 30 minutes after start of high-fat (753 kcal, 55.3% of kcal from fat) breakfast.

Regimen D One venetoclax 100 mg film-coated tablet (manufactured in North Chicago, IL, USA) administered approximately 30 minutes after start of a low-fat (512 kcal, 25.1% of kcal from fat) breakfast.

Pharmacokinetic Results

The mean (+ standard deviation [SD]) plasma concentration-time profiles for Regimens B and D are presented in Figure 2 on a log-linear scale.

Figure 2. Mean + SD Venetoclax Plasma Concentration-Time Profiles for Regimens B and D, Log-Linear Scale



The mean ± standard deviation (SD) pharmacokinetic parameters of venetoclax after administration of each of Regimens B and D are shown in Table 8.

Table 8. Mean ± SD Pharmacokinetic Parameters of Venetoclax for Regimens B and D

Regimens		
Pharmacokinetic Parameters (units)	B: 100 mg Venetoclax Tablet Ireland, Low-Fat (Test) (N = 24)	D: 100 mg Venetoclax Tablet Low-Fat (Reference) (N = 24)
T_{max}[a] (h)	6.0 (4.0 – 10.0)	6.0 (4.0 – 10.0)
C_{max} (µg/mL)	0.54 ± 0.21	0.53 ± 0.23
AUC_t (µg•h/mL)	7.45 ± 3.05	7.25 ± 3.52
AUC_∞ (µg•h/mL)	7.79 ± 3.20	7.59 ± 3.77
$t_{1/2}$[b] (h)	18.0 ± 5.6	18.6 ± 5.0
CL/F[c] (L/h)	16.0 ± 9.2	18.5 ± 12.6
Vdβ/F[c] (L)	411 ± 168	503 ± 360

For T_{max}, median (minimum – maximum) are reported. Harmonic mean ± pseudo-standard deviation; evaluations of $t_{1/2}$ were based on statistical tests for β. Parameter was not tested statistically.

The test statistics for period and sequence effects were not statistically significant for any of the tested pharmacokinetic parameters ($p \geq 0.0832$). There were no statistically significant differences in mean C_{max}, AUC, T_{max}, and β between Regimen B and D for the pharmacokinetic parameters tested ($p \geq 0.4230$).

Conclusions

Compared to the tablets manufactured in the US (Regimen D, reference) the site of manufacture of the venetoclax film-coated tablets used in clinical trials, tablets manufactured in Ireland (Regimen B, test), the site of manufacture of the venetoclax film-coated tablets proposed for marketing, exhibited similar exposures with point estimates of C_{max} and AUC ratios of 1.070 to 1.083. The upper bounds of the 90% confidence intervals for C_{max}, AUC_t, and AUC_∞ ratios extended slightly above 1.25 (1.275 to 1.281). Food increased venetoclax exposure compared to fasting conditions in healthy subjects. Low-fat meals increased C_{max} and AUC by approximately 3.4-fold. High-fat meals increased C_{max} and AUC by approximately 5.2-fold. High-fat meals increased exposure (C_{max} and AUC) by approximately 1.5-fold compared to low-fat meals in healthy subjects.

4.2.2.3. Study M13-363: Absorption, Distribution, Metabolism and Excretion (ADME) study of [^{14}C]ABT-199 in Healthy Female Subjects of Non-Childbearing Potential Following a Single Oral Dose Administration

Study Objectives and Design

The objective of this study was to investigate the disposition of [^{14}C]ABT-199 in approximately four healthy female subjects of non-childbearing potential following a single oral dose of [^{14}C]ABT-199.

This was a Phase I, single radio-labelled dose, open-label, single centre, mass balance study. A total of four female subjects of non-childbearing potential, in general good health, were selected to participate in the study according to the selection criteria.

The study was designed to enrol approximately 4 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

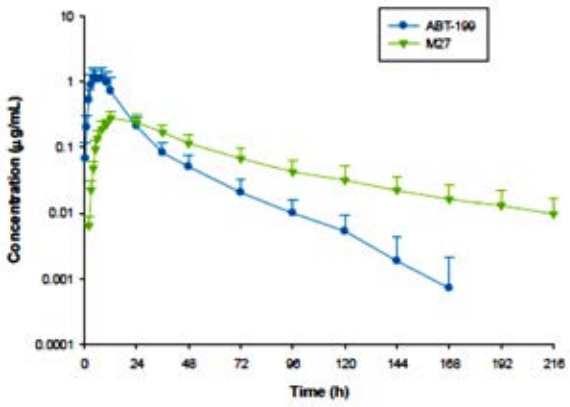
On the morning of Study Day 1, subjects received a single oral dose of [^{14}C]ABT-199 approximately 30 minutes after completion of a moderate-fat breakfast. The study drug, [^{14}C]ABT-199 (200 mg active, 100 µCi), was administered orally via syringe as an approximately 4 mL liquid solution. The dose of the study drug was taken orally, followed by approximately 240 mL of additional water. The radioactive dose level was approximately 100 µCi per subject.

Subjects were confined to the study site and supervised beginning on Study Day –1 and continuing through 216 h after dosing and completion of study activities. Excreta and blood for the determination of the disposition of [^{14}C]ABT-199 were collected. Safety was assessed throughout the study.

Pharmacokinetic Results

The mean (+ SD) plasma concentration-time profiles of ABT-199 and M27 metabolite are presented on a log-linear scale in Figure 3.

Figure 3. Mean (+ SD) ABT-199 and M27 Metabolite Plasma Concentration-Time Profiles, Log-Linear Scale



The mean and coefficient of variation (%CV) pharmacokinetic parameters of ABT-199 and M27 metabolite after administration of a single dose of 200 mg ABT-199 to healthy subjects are shown in Table 9.

Table 9. Mean (%CV) Pharmacokinetic Parameters of ABT-199 and M27 Metabolite After a 200 mg Dose of ABT-199

Parameters (units)	ABT-199 (N = 4)	M27 (N = 4)	Metabolite/Parent Ratio
T_{max}[a] (h)	5 (4 – 8)	12 (12 – 12)	2.5 (1.5 – 3)
C_{max} (µg/mL)	1.41 (30)	0.28 (27)	0.20 (14.6)
$t_{1/2}$[b] (h)	23.3 (4.4)	58.8 (32)	2.54 (29)
AUC_t (µg•h/mL)	20.0 (35)	14.9 (32)	0.76 (18)
AUC_∞ (µg•h/mL)	20.1 (35)	15.8 (32)	0.80 (19)

For T_{max}, median (minimum – maximum) are reported. Harmonic mean (%CV)

Conclusions

Nearly all (> 99.9%) administered radioactive dose was recovered in faeces and limited radioactivity (< 0.1%) was found in urine. The mean percentages of radioactive dose recovered in faeces at 24, 48, 72, 96, 168 and 216 h were 1.06%, 12.9%, 61.2%, 81.2%, 99.4%, and 100%, respectively. Unchanged ABT-199 accounted for 72.6% of the total radioactivity in pooled plasma while metabolites M27, Unknown 1, and Unknown 2 accounted for 12%, 9.0%, and 6.4% of the total plasma radioactivity. About 80% of the administrated radioactive dose was excreted in faeces as ABT-199 metabolites, suggesting that a substantial portion of the dose was cleared by metabolism. In faeces, unchanged parent was the main component with a mean of about 20.8% of the administered radioactive dose, followed by M34 (16.9%) and M30 (12.9%). Many other minor metabolites were detected in faeces including M2, M5, M14, M16, M17, M18, M23, M27, M31, M32, M33, M35, M36, M37, Unknown 3 and Unknown 4, each representing < 9% of the administered dose. Metabolites in urine were not quantified and did not undergo structure elucidation since a very limited amount (< 0.1%) of radioactive dose was recovered in the urine. Thus, ABT-199 is largely cleared as metabolites in the faeces and any potential renal excretion is very limited.

4.2.2.4. Study M14-497: A Phase I Open-Label Study to Assess the Effect of Rifampin on the Pharmacokinetics of ABT-199 in Healthy Female Subjects of Non-Childbearing Potential

Study Design and Objectives

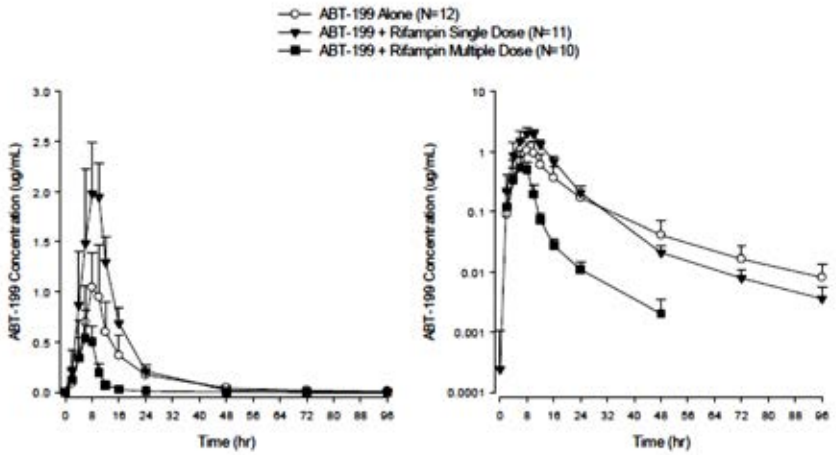
The primary objective of this study was to investigate the effect of rifampin, a potent CYP3A inducer and OATP1B1 inhibitor on the pharmacokinetics of ABT-199 in healthy female subjects of non-childbearing potential. The secondary objective was to determine the safety of ABT-199 when administered alone and in combination with rifampin.

This was a Phase I, open-label study enrolling 12 adult healthy female subjects of non-childbearing potential according to selection criteria. The study consisted of 2 Periods. There was a minimum washout period of 8 days separating the ABT-199 dose in Period 1 with the first dose of ABT-199 and rifampin in Period 2. ABT-199 was administered orally (with approximately 240 mL of water). The subjects were administered ABT-199 approximately 30 minutes after the start of a moderate-fat breakfast. Each subject received a single 200 mg dose of ABT-199 on Period 1 Day 1, Period 2 Day 1, and Period 2 Day 14, and 600 mg once daily (QD) dose of rifampin on Period 2 Day 1 and Period 2 Days 5 through 17. On Period 2 Day 5, the 96-h pharmacokinetic sample after the Period 2 Day 1 ABT-199 dose was obtained prior to administration of rifampin. Each dose of rifampin was administered with approximately 240 mL of water after at least 2 h of fasting; the subject continued to fast for another 2 h before completion of a moderate-fat breakfast. The exceptions were on Period 2 Day 1 and Period 2 Day 14, when rifampin was administered at the same time or within 5 minutes after the ABT-199 dose. Pharmacokinetic samples were collected prior to ABT-199 dosing (pre-dose/0-h) and at 2, 4, 6, 8, 10, 12, 16, 24, 48, 72, and 96 h after dosing on Period 1 Day 1, Period 2 Day 1 and Period 2 Day 14. A pharmacogenetic sample was collected prior to ABT-199 dosing on Period 1 Day 1.

Pharmacokinetic Results

The mean + SD plasma concentration-time profiles for ABT-199 are presented in Figure 4 on linear and log-linear scales.

Figure 4. Mean + SD ABT-199 Plasma Concentration-Time Profiles When ABT-199 Was Administered Alone and with Rifampin, Linear and Log-Linear Scales



For the relative bioavailability analysis of log-transformed C_{max}, AUC_t and AUC_∞, the 90% confidence intervals and the corresponding point estimates of relative bioavailability of ABT-199 is shown in Table 10.

Table 10. Relative Bioavailability of ABT-199 and 90% Confidence Intervals for the Bioavailability Assessment

				Relative Bioavailability	
		Central Value			
Regimens Test vs. Reference	Pharmacokinetic Parameter	Test	Reference	Point Estimate	90% Confidence Interval
		P2/D1	P1/D1		
B: Venetoclax + rifampin (single) vs. A: Venetoclax	C_{max}	2.15	1.04	2.06	1.729 – 2.445
	AUC_t	23.9	13.3	1.80	1.518 – 2.126
	AUC_∞	24.0	13.5	1.78	1.501 – 2.105
		P2/D14	**P1/D1**		
C: Venetoclax + rifampin (multiple) vs. A: Venetoclax	C_{max}	0.61	1.04	0.58	0.484 – 0.693
	AUC_t	3.8	13.3	0.29	0.242 – 0.343
	AUC_∞	3.9	13.5	0.29	0.241 – 0.342

Regimen A: Venetoclax 200 mg on Period 1 Day 1 under non-fasting conditions (Reference). Regimen B: Venetoclax 200 mg + rifampin 600 mg on Period 2 Day 1 under non-fasting conditions (Test). Regimen C: Venetoclax 200 mg on Period 2 Day 14 + rifampin 600 mg Period 2 Days 5 through 17 under non-fasting conditions (Test).

Conclusions

After a single rifampin dose, ABT-199 C_{max} and AUC_{∞} increased 106% and 78%, respectively. In contrast, multiple doses of rifampin decreased ABT-199 C_{max} and AUC_{∞} by approximately 42% and 71%, respectively. The decrease in both exposure and half-life of ABT-199 and M27 metabolite further confirms the key role of CYP3A4 in ABT-199 metabolism. Additionally, rifampin's induction of the efflux transporter, P-gp, may have also contributed to the observed decrease in ABT-199 exposure.

4.2.2.5. Study M15-065: A Phase I Open-Label Study to Assess the Effect of ABT-199 on the Pharmacokinetics of Warfarin in Healthy Female Subjects of Non-Childbearing Potential

Study Design and Objectives

This Phase I, open-label study was conducted according to a two-period, single-arm, non-randomised design. The study was designed to enrol up to 12 adult female subjects of non-childbearing potential in general good health based on the selection criteria. Eight subjects (N = 8) were enrolled in the study, with 3 subjects completing both periods and 5 subjects completing only Period 1.

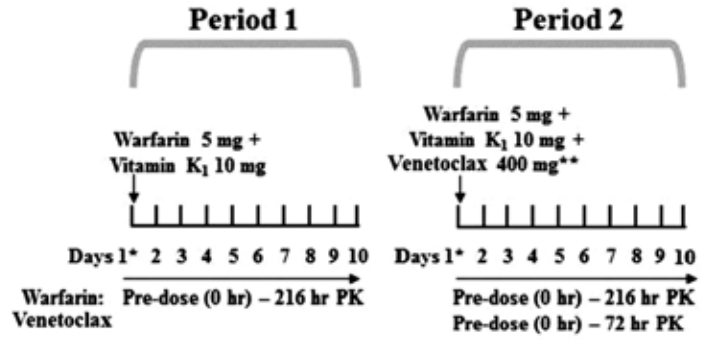
A description of study drug administration in Period 1 and 2 follows.

Period 1 A single 5 mg dose of warfarin and a single 10 mg dose of vitamin K1 administered approximately 30 minutes after the start of a moderate-fat breakfast on Day 1.

Period 2 A single 5 mg dose of warfarin and a single 10 mg dose of vitamin K1 administered approximately 30 minutes after the start of a moderate-fat breakfast on Day 1. A single 400 mg dose of venetoclax administered at the same time as the warfarin dose (approximately 30 minutes after the start of a moderate-fat breakfast on Day 1).

Each administration of warfarin and vitamin K1 with or without venetoclax was taken with a total of approximately 240 mL of water. There was a minimal washout period of 14 days separating the warfarin dose in Period 1 and the doses of warfarin and venetoclax in Period 2 (Figure 5).

Figure 5. Warfarin/Venetoclax Dosing Schematic



PK = pharmacokinetic. * There was a minimal 14-day washout between Period 1 Day 1 and Period 2 Day 1. ** After completion of Period 2 Day 10 by the first 3 subjects, venetoclax dosing was stopped for subsequent subjects

Pharmacokinetic Results

The mean + standard deviation (SD) plasma concentration-time profiles for R-warfarin are presented on linear and log-linear scales in Figure 6 and for S-warfarin in Figure 7.

Figure 6. Mean + SD R-Warfarin Plasma Concentration-Time Profiles Following Administration of Warfarin Alone and with Venetoclax, Linear and Log-Linear Scales

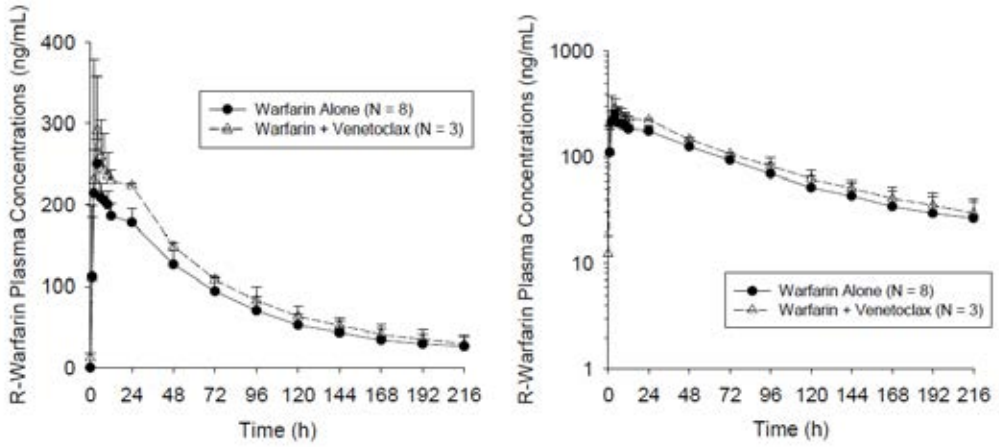
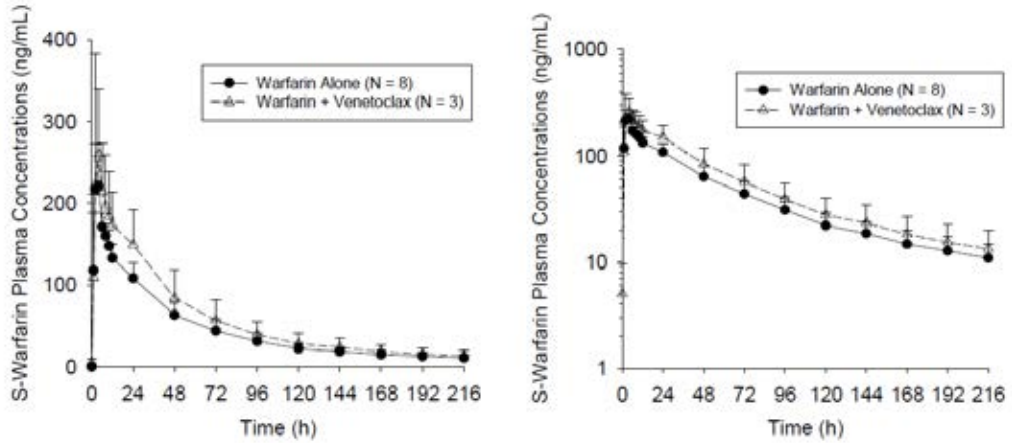


Figure 7. Mean + SD S-Warfarin Plasma Concentration-Time Profiles Following Administration of Warfarin Alone and with Venetoclax, Linear and Log-Linear Scales



The mean ± SD pharmacokinetic parameters of R- and S-warfarin after administration of each regimen are shown in Table 11.

Table 11. Mean ± SD Pharmacokinetic Parameters of R- and S-Warfarin for a Single Oral Dose of 5 mg Warfarin Administered Alone and with a Single Oral Dose of Venetoclax

Regimens[a]		
Pharmacokinetic Parameters (units)	Warfarin Alone Period 1 Day 1 (N = 8))	Warfarin + Venetoclax Period 2 Day 1 (N = 3)
	R-Warfarin	
T_{max}[b] (h)	4.0 (2.0 – 4.0)	4.0 (2.0 – 6.0)
C_{max} (µg/mL)	252 ± 30	298 ± 57*
AUC_t (µg•h/mL)	17720 ± 2676	21236 ± 1182*
AUC_∞ (µg•h/mL)	21278 ± 4520	25396 ± 3962
$t_{1/2}$[c] (h)	85.3 ± 35.8	85.2 ± 22.4
CL/F[d] (L/h)	0.12 ± 0.02	0.10 ± 0.01
	S-Warfarin	
T_{max}[b] (h)	3.0 (1.0 – 4.0	4.0 (2.0 – 4.0)
C_{max} (µg/mL)	239 ± 33	269 ± 92

	Regimens[a]	
AUC_t (µg•h/mL)	9768 ± 1972	12561 ± 4661*
AUC_∞ (µg•h/mL)	11261 ± 2640	14266 ± 5536*
$t_{1/2}$[c] (h)	79.6 ± 29.4	87.7 ± 3.0
CL/F[d] (L/h)	0.23 ± 0.06	0.20 ± 0.09

Warfarin 5 mg was administered with 10 mg of vitamin K1 as a single dose on Period 1 Day 1 and Period 2 Day 1. Venetoclax 400 mg was administered as a single dose on Period 2 Day 1 at the same time the warfarin dose was administered. For T_{max}, median (minimum – maximum) was reported. Harmonic mean ± pseudo-standard deviation; evaluations of $t_{1/2}$ were based on statistical tests for β. Parameter not tested statistically. * Statistically significantly different from warfarin alone ($p < 0.05$).

Conclusions

Following co-administration of a single dose of 400 mg venetoclax with warfarin, R- and S-warfarin C_{max} and AUC_∞ increased by approximately 18% to 28%.

4.2.2.6. Study M13-364: A Phase I Study to Assess the Effect of Ketoconazole on the Pharmacokinetics of ABT-199

Study Design and Objectives

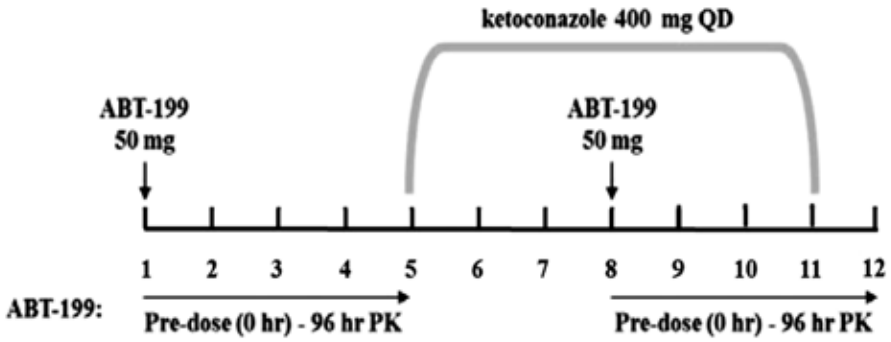
The primary objective of this study was to investigate the effect of ketoconazole, a potent CYP3A inhibitor, on the pharmacokinetics of ABT-199. The secondary objective was to determine the safety of ABT-199 when administered alone and in combination with ketoconazole.

This was a Phase I, open-label study that planned to enroll up to 15 adult subjects with relapsed or refractory NHL (excluding CLL, SLL, and MCL). The pharmacokinetic (PK) profile of the first 3 subjects to complete all 12 days of the study was to be used to adjust, if necessary, the initial ABT-199 (50 mg) dose to be evaluated. Enrollment was considered to be complete when 12 subjects completed all 12 days of the study, at the selected ABT-199 dose level, to allow for a minimum of 8 subjects to be evaluable for PK analysis. The study was designed to enroll up to 15 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects were enrolled, there was a possibility that additional subjects in screening would not be enrolled.

Each subject received a single 50 mg dose of ABT-199 on Day 1 and Day 8, and 400 mg once daily (QD) dose of ketoconazole on Days 5 through 11. On Day 8, ketoconazole was administered at the same time or within 5 minutes after the ABT-199 dose in the clinic. ABT-199 was administered orally with approximately 240 mL of water, after completion of a standard low-fat breakfast. Venous blood samples from which plasma was obtained for pharmacokinetic (PK) assay of ABT-199 and M27 metabolite were collected on Day 1 and Day 8.

A schematic of the study design is shown in Figure 8.

Figure 8. ABT-199/Ketoconazole Dosing Schematic



Pharmacokinetic Results

Co-administration of ketoconazole with venetoclax in 11 subjects resulted in a 2.3-fold increase in venetoclax C_{max} and a 6.4-fold increase in AUC_{∞}, while the M27 metabolite C_{max} and AUC_t decreased by approximately 50% and 30%, respectively (Table 12).

Table 12. Relative Bioavailability and 90% Confidence Intervals for Venetoclax and M27 Metabolite

Relative Bioavailability					
		Central Value			
Regimens[a] Test vs. Reference	Pharmacokinetic Parameter	Test	Reference	Point Estimate	90% Confidence Interval
Venetoclax					
Venetoclax + Ketoconazole (Study Day 8) vs. Venetoclax Alone (Study Day 1)	C_{max}	0.461	0.198	2.323	1.996 – 2.702
	AUC_t	17.887	3.803	4.703	3.549 – 6.233
	AUC_{∞}	25.366	3.961	6.403[b]	4.472 – 9.168
M27 Metabolite					
Venetoclax + Ketoconazole (Study Day 8) vs. Venetoclax Alone (Study Day 1)	C_{max}	0.009	0.018	0.499	0.419 – 0.595
	AUC_t	0.694	0.968	0.717	0.634 – 0.812
	AUC_{∞}	2.356	1.308	1.801[c]	0.961 – 3.376

Venetoclax 50 mg administered on Study Day 1 under non-fasting conditions (Reference). Ketoconazole 400 mg QD administered on Study Days 5 through 11, and venetoclax 50 mg administered on Study Day 8 under non-fasting conditions (Test). N = 10. N = 4.

Ketoconazole is a potent and selective inhibitor of CYP3A, the primary cytochrome isozyme responsible for the metabolism of ABT-199 and M27. Ketoconazole also inhibits P-glycoprotein (P-gp), which can also alter drug disposition. Ketoconazole co-administration increased ABT-199 C_{max} (2.3-fold), AUC_{∞} (6.4-fold) and $t_{1/2}$ (approximately two times longer). M27 metabolite mean C_{max} and AUC_t decreased by approximately 50% and 30%, respectively, after co-

administration of ABT-199 with multiple doses of ketoconazole compared to administration of ABT-199 alone. These results are consistent with CYP3A inhibition of ABT-199 metabolism and formation of M27. Inhibition of P-gp may have also contributed to the increase in ABT-199 exposure.

4.2.2.7. R&D/15/0256: Population Pharmacokinetics of Venetoclax in Relapsed or Refractory (R/R) Chronic Lymphocytic Leukemia (CLL), Non-Hodgkin's Lymphoma (NHL) and Healthy Subjects.

Study Design and Objectives

To characterise the population pharmacokinetics (PKs) of venetoclax in R/R CLL/small lymphocytic lymphoma (SLL), NHL, and healthy subjects in order to examine the sources of variability in drug concentrations and identify demographic, pathophysiologic and treatment factors that may contribute to the variability in the pharmacokinetics of venetoclax.

All R/R CLL/SLL, NHL and healthy subjects enrolled in Studies M12-175, M13-364, M13-365, M13-982, M14-032, M14-253, M14-497 and M15-101 who had at least one measurable venetoclax concentration by the enrolment and interim data cut dates, if applicable. In total, 505 subjects (66.5% CLL/SLL, 23.4% NHL, and 10.1% healthy) were included in the analysis.

A nonlinear mixed-effects model was developed to characterise the population pharmacokinetics of venetoclax after oral administration of doses ranging from 10 to 1200 mg in 505 subjects.

Results

A two-compartment PK model with first-order absorption and elimination adequately described the venetoclax plasma concentration-time data. The inter-individual variability CVs for CL/F, V2/F and F1 in the base model, which only accounted for dose and food effects were 47.7%, 58.0% and 31.3%, respectively. The CV for the intra-subject residual proportional variability was approximately 48.3%. The complete identified sources of variability in the population pharmacokinetic final model were:

- moderate and strong CYP3A inhibitors on apparent clearance (CL/F)
- rituximab co-administration and co-administration of drugs reported in the literature as OATP1B3 transporter inhibitors on CL/F
- sex and subject population on apparent central volume of distribution (V2/F)
- dose and food (fasted, fed, low-, moderate- and high-fat meals) on relative bioavailability (F1)

Upon inclusion of the above sources of variability, the remaining unexplained inter-individual variability for CL/F and V2/F was reduced to 40.7% and 47.7%, respectively. Visual predictive checks indicated that the final model incorporating these covariates described the central tendency of the data well and the variability (5th and 95th percentile) of the data reasonably. The non-parametric bootstrap evaluation demonstrated good agreement between the estimated parameter values. The parameter estimates and key covariate effects with confidence intervals (CI) were:

- CL/F: 447 (95% CI: [416 – 478]) L/day
- Weak CYP3A inhibitors and inducers had no effect on CL/F
- Moderate CYP3A inhibitors decreased CL/F by 16% (95% CI: [9% – 23%])
- Strong CYP3A inhibitors decreased CL/F by 82% (95% CI: [79% – 84%])
- Rituximab co-administration increased CL/F by 22% (95% CI: [15% – 29%])

- Drugs reported in the literature as OATP1B3 hepatic uptake transporter inhibitors decreased CL/F by 15% (95% CI: [10% – 19%])
- V2/F: 118 (95% CI: [86.2 – 150]) L in male healthy subjects
- Females had V2/F that was 32% (95% CI: [23% – 41%]) less than males
- Subjects with CLL/SLL and NHL had a V2/F that was 71% (95% CI: [29% – 113%]) more than healthy subjects

F1 (relative bioavailability):

Administration with a low-fat meal increased F1 by 2.99 (95% CI: [2.94 – 3.04])-fold relative to the fasting-state:

- The fed state (without specification of fat-content) increased F1 by 3.67 (95% CI: [3.35 – 3.98])-fold relative to the fasting-state
- Administration with moderate- and high-fat meal increased F1 by 3.91 (95% CI: [3.27 – 4.58])- and 4.27 (95% CI: [4.17 – 4.37])-fold, respectively, relative to administration with a low-fat meal
- An increase in the dose by 2-fold decreased F1 by 11.7% (95% CI: [11.2% – 12.2%])
- A decrease in the dose by 0.5-fold increased F1 by 13.3% (95% CI: [12.7% – 13.9%])
- KA: 3.72 (95% CI: [3.42 – 4.02]) 1/day

Comment: The population estimate for the terminal phase elimination half-life was approximately 26 h, which supports the proposed daily dosing.

Covariates of Special Interest

Age

Age ranged 25 – 88 years across the population, with a median of 65 years old. Most subjects were > 60 years of age. Age was tested as a covariate on CL/F and V2/F in the stepwise model building procedure, but it did not reach statistical significance ($P < 0.01$) during the forward inclusion process. Therefore, it was not included as covariate in the final model.

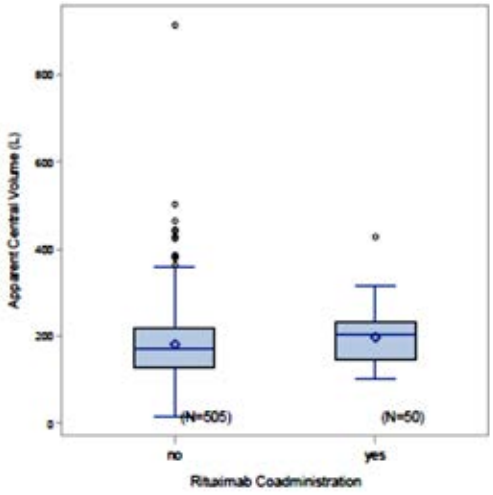
Sex

Approximately 60% of the subjects were male. Sex was tested as a covariate on CL/F in the stepwise model building procedure, but it did not reach statistical significance ($P < 0.01$) during the forward inclusion process. Therefore, it was not included as covariate on CL/F in the final model.

Rituximab

Rituximab co-administration was tested as a covariate on CL/F in the stepwise model building procedure. It did reach statistical significance in both the forward inclusion ($P < 0.01$) and backward elimination ($P < 0.001$) procedures; therefore, it was included as covariate on CL/F in the final model. A boxplot of the post hoc EBEs using the final model displays the relationship between CL/F and rituximab co-administration (Figure 9), with rituximab co-administration estimated to increase venetoclax CL/F by 1.22 (95% CI: [1.15 – 1.29])-fold (that is, 22% higher). The corresponding point estimates of the apparent clearance without and with rituximab are 447 and 545 L/day, respectively.

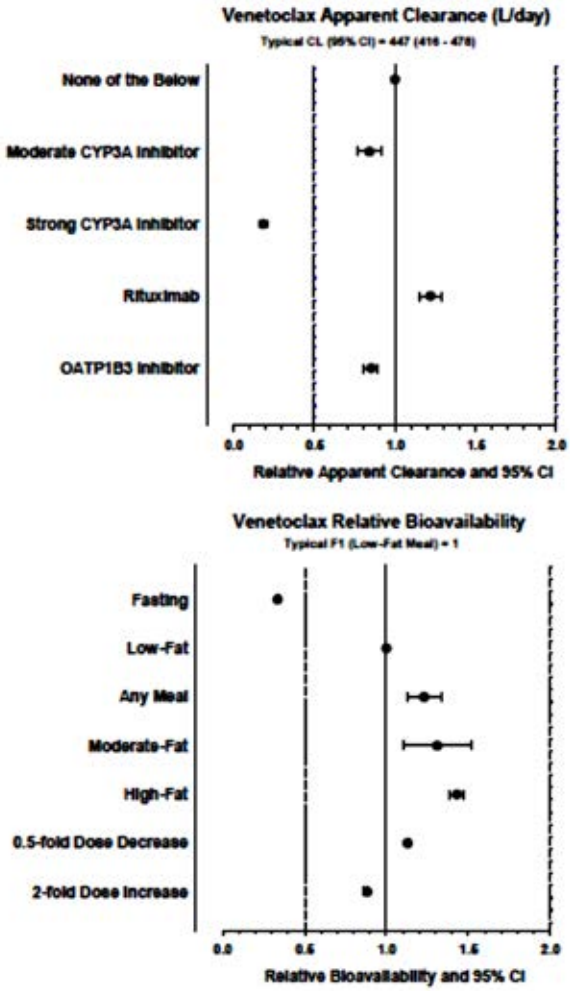
Figure 9. Boxplot of the Post Hoc Apparent Clearance (CL/F) by Rituximab Co-Administration



Comment: Only 50 subjects (9.9%) were administered rituximab, with all but 4 of these subjects from Study M13-365.

A schematic forest plot of the covariates incorporated into the final model that affected AUC and the magnitude of their effects (point estimate and 95% CI) are displayed in Figure 10.

Figure 10. Forest Plot of the Covariates that Affect AUC



The factor effects of the final model covariates on apparent clearance (CL/F, top), and relative bioavailability (bottom, F1) are displayed.

Conclusions

The population pharmacokinetics of venetoclax in R/R CLL/SLL, NHL and healthy subjects were characterised. A two-compartment PK model with first-order absorption and elimination adequately described the venetoclax plasma concentration-time data. The identified sources of variability in the population pharmacokinetics were: moderate and strong CYP3A inhibitors, rituximab co-administration, and co-administration of medications reported in the literature as OATP1B3 transporter inhibitors on apparent clearance, sex and subject population (healthy versus CLL/SLL/NHL) on the apparent volume of distribution of the central compartment, and dose and food on relative bioavailability.

Bodyweight, age, sex, race, subject population, mild and moderate hepatic and renal impairment, and weak CYP3A inhibitors and inducers had no effect on clearance. Moderate inhibitors of CYP3A had a minimal effect (0.5 – 2.0 fold) on venetoclax clearance, while strong inhibitors decreased clearance to approximately 0.2-fold of the clearance without CYP3A inhibitors. Rituximab co-administration and administration of medications reported in the literature as OATP1B3 transporter inhibitors also had a minimal effect on clearance. The covariate effects on volume do not affect venetoclax AUC and, hence, dose adjustments for sex and subject population are not necessary. There were no identified differences in the pharmacokinetics between CLL/SLL and NHL subjects. The dose dependency of the relative bioavailability of venetoclax was minimal and not of clinical concern. Administration of venetoclax with food was estimated to increase the relative bioavailability from 2.99- to 4.27-fold compared to the fasting-state. Therefore, venetoclax should be administered with food, without regard to fat content, to ensure adequate and consistent bioavailability.

Overall, the population pharmacokinetic model successfully characterised venetoclax plasma concentrations over time and was able to identify the key intrinsic and extrinsic factors affecting venetoclax pharmacokinetics. The model is appropriate to use for simulations and to evaluate the exposure-response relationship of venetoclax.

4.2.3. Rationale for Dose Selection

The recommended venetoclax dosage was selected based upon an integrated assessment of data from in vitro, preclinical, and clinical studies and is as follows:

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

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

Treatment should continue until disease progression or venetoclax is no longer tolerated by the patient.

Exposure-response analyses using data from four studies in subjects with cancer (Studies M13-982, M12-175, M14-032 and M13-365) were summarized. Nonlinear mixed-effects population pharmacokinetic/pharmacodynamic (PK/PD) models were developed to separately characterise the exposure-efficacy relationship between venetoclax concentrations and total circulating lymphocytes and tumour size in subjects with CLL/SLL. Indirect response models with stimulation of output adequately described both the circulating lymphocyte and tumour size responses to plasma venetoclax concentrations. A constant minimum lymphocyte term was also incorporated into the lymphocyte PK/PD model to account for a lymphocyte sub-population unaffected by venetoclax. The population linear venetoclax effect (Eslope) estimates were 138 (95% CI: [66.1 – 851]) and 6.84 (95% CI: [5.24 – 7.75]) mL/µg for lymphocytes and tumour size, respectively, indicating that lymphocytes are more sensitive than tumours to the

effects of venetoclax. Based on the model parameters, estimates in typical subjects average steady-state venetoclax concentrations of 0.00863 and 0.146 µg/mL decrease lymphocytes and tumour size by 50%, respectively.

The half-life of CLL cells was estimated at 204 (95% CI: [93.5 – 1359]) days. No covariates were incorporated into the lymphocyte model during the stepwise forward inclusion, backward elimination procedure, indicating the evaluated covariates were not influential in describing the inter-individual variability in lymphocyte response. Bodyweight was identified to have an impact on the baseline tumour size, with heavier subjects having a larger baseline tumour size. The 17p deletion somatic mutation was not identified to influence the responsiveness of lymphocytes or tumour size to venetoclax.

Simulations of the objective response rate (ORR) using the final lymphocyte and tumour size models indicated that a dosage regimen of 400 mg QD in patients with CLL/SLL maximises the probability of a typical subject achieving ORR at > 80%. By 6 months of venetoclax treatment, the ORRs reached 80.9% (95% CI: [77.5 – 84.0%]), 84.8% (95% CI: [81.5 – 88.0%]), and 85.5% (95% CI: [82.6 – 88.4%]) at the 200, 400 and 600 mg dosage regimens, respectively. Long-term maximum effects were similar for all dosage regimens to the ORR of 85.7% (95% CI: [82.6 – 88.6%]) achieved with 400 mg QD. A 0.5- and 2.0-fold change in exposure from that achieved in a typical subject at the 400 mg QD dosage regimen is predicted to result in a 2.3% (95% CI: [–2.4 – 7.1%]) decrease and a 0.0% (95% CI: [–4.5 – 4.1%]) increase, respectively, from the ORR expected to be achieved long term with a standard exposure.

In the Phase I study, M12-175, the first dose was 200 mg per day, and patients received a single initial dose followed by a washout period of at least 72 h, which was followed by continuous daily administration. The occurrence of laboratory changes associated with tumour lysis in the first three patients led to the introduction of stepwise intra patient increases in dose (ramp-up) to the designated group dose for the subsequent dose-escalation and expansion cohorts, respectively. To explore whether dose influenced the durability of disease control, patients were grouped according to the assigned dose (< 400 mg, 400 mg, and > 400 mg), and progression-free survival was analysed to the point at which data for the 400-mg group were mature. The 15-month progression free estimates were 58% (95% CI, 34 to 77) for the patients who received less than 400 mg per day, 69% (95% CI, 55 to 79) for those who received 400 mg per day, and 77% (95% CI, 56 to 89) for those who received more than 400 mg per day. Similar patterns were observed for the duration of response and the time to progression.

4.3. Evaluator's overall conclusions on pharmacokinetics

The application included detailed characterisations of the clinical pharmacology of venetoclax, which were based on preclinical studies and clinical development in Phase I and II studies. Pharmacokinetic assessments included single- and multiple-dose PK, dose proportionality, accumulation ratio, impact of renal and hepatic dysfunction, and Drug-drug interaction studies with ketoconazole, rifampin and warfarin were conducted to provide dosing recommendations for venetoclax in subjects who were concomitantly taking CYP3A inhibitors, CYP3A inducers or warfarin.

All studies were conducted as planned and protocol deviations and violations were provided. Collection and storage of samples were described and adequate. The assays used to determine plasma concentrations were adequately described and validated. For all provided studies inclusion/exclusion criteria were appropriate and compliance with treatment was acceptable

Following multiple-dose administration, the maximum plasma concentration of venetoclax was attained by 5 to 8 h. The harmonic mean terminal half-life ($t_{1/2}$) ranged from 17 to 41 h following a single oral dose of venetoclax (Study M12-175), which supported the proposed daily dosing. In subjects with CLL, venetoclax showed minimal accumulation, and steady-state AUC increased proportionally over the dose range of 150 to 800 mg. Venetoclax was administered

with food in all clinical studies, as food increased the bioavailability of venetoclax by approximately 3- to 5-fold. Venetoclax is highly bound to plasma proteins with the unbound fraction < 0.01, and it is primarily eliminated as metabolites in faeces with negligible renal elimination (< 0.1%).

M27 was identified as a major metabolite with an inhibitory activity against BCL -2 that is at least 58-fold lower than venetoclax in vitro. Venetoclax and M27 are predominantly metabolized by cytochrome P450 CYP3A4 in vitro.

Population pharmacokinetic analyses using data from five studies in subjects with cancer (Studies M13-982, M12-175, M14-032, M13-365 and M13-364) and three studies in healthy subjects (Studies M14-253, M14-497 and M15-101), was able to characterise venetoclax plasma concentrations over time and identify the key intrinsic and extrinsic factors affecting venetoclax pharmacokinetics. The complete identified sources of variability in the population pharmacokinetic final model were:

- moderate and strong CYP3A inhibitors on apparent clearance (CL/F)
- rituximab co-administration and co-administration of drugs reported in the literature as OATP1B3 transporter inhibitors on CL/F
- sex and subject population on apparent central volume of distribution (V2/F)
- dose and food (fasted, fed, low-, moderate- and high-fat meals) on relative bioavailability (F1)

Both sex and subject population were identified as covariates in the population PK model; however, neither of these covariates impacted venetoclax clearance. Therefore, these covariates have no effect on the AUC (main measure of exposure), and based on these intrinsic factors, no dose adjustment is necessary. The differences between subjects with CLL/SLL and NHL compared to healthy subjects was due to a lower C_{max} in subjects with cancer, which was likely due to more frequent sampling in studies in healthy subjects better capturing C_{max}.

No specific clinical studies were conducted in subjects with renal impairment. The population pharmacokinetic analysis dataset included 211 subjects with mild renal impairment ($60 \leq CL_{cr} < 90$ mL/min), 83 subjects with moderate renal impairment ($30 \leq CL_{cr} < 60$ mL/min), and 210 subjects with normal renal function ($CL_{cr} \geq 90$ mL/min). The population PK analysis indicated no relationship between CL/F and renal function or creatinine clearance.

No specific clinical studies were conducted in subjects with hepatic impairment. The population pharmacokinetic analysis dataset included 69 subjects with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] [1 mg/dL] and AST > ULN [40 IU/L], or total bilirubin > 1.0 to 1.5 times ULN [> 1 to 1.5 mg/dL] and any AST value), 7 subjects with moderate hepatic impairment (total bilirubin > 1.5 to 3 times ULN [> 1.5 to 3.0 mg/dL] and any AST value), and 429 subjects with normal hepatic function (total bilirubin ≤ ULN [1 mg/dL] and AST ≤ ULN [40 IU/L]). The final model indicated no relationship between CL/F or V2/F and hepatic function. Similarly, baseline ALT, AST, and bilirubin were also tested as covariates on CL/F and no statistically significant relationship between them was observed.

For the pivotal Study M13-982, at the time of dose selection there was limited complete remission data therefore the dose was selected based on ORR alone. A repeated measures logistic regression analysis between exposure and objective response conducted at the time of dose selection predicted a difference in objective response rates (ORR) between the 400 mg and 600 mg doses at early time points; however, the difference was negligible after 24 weeks of treatment. A population PK/PD exposure response analysis on lymphocytes and tumour size was also conducted to further refine the dose selection. The established population PK/PD models based on lymphocyte and tumour response were subsequently used to predict the ORR. Based on these simulations, 84.0% of subjects in the 200 mg regimen, 87.8% of subjects in the

400 mg regimen, and 89.9% in the 600 mg regimen would achieve OR by Week 24. By Week 12, the effect plateaued due to reaching a steady state with the designated cohort dose.

In M12-175, overall response rates were similar among patients who initially received doses ranging from 400 to 1200 mg per day in the dose-escalation cohort. The selection of 400 mg per day as the dose for ongoing evaluation was informed by the balance of overall response and safety data; the selection of this dose was subsequently supported by the safety and efficacy analyses of data from the expansion cohort after a minimum of 15 months of follow-up.

The proposed Product Information is an adequate summary of the PK presented in the submission.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Venetoclax-related decreases in lymphocytes were observed in animals and in humans, consistent with the mechanism-related pharmacologic effect of selective Bcl-2 inhibition. Thus, lymphocyte decreases were an expected pharmacodynamic effect of venetoclax.

Pharmacogenetic analysis and a portion of the pharmacodynamic analyses were optional procedures, and consent for these analyses was included with the protocol informed consent, for studies M12-175 and M13-982. The exploratory objectives of the M13-365 study were to assess pharmacodynamics and pharmacogenetics of the combination of venetoclax and rituximab and MRD in the peripheral blood and bone marrow either by flow cytometry or real-time PCR.

Study R&D/15/0255 'Exposure-Efficacy Relationship of Venetoclax in Subjects with Relapsed or Refractory (R/R) Chronic Lymphocytic Leukemia (CLL) and the Exposure-Safety Relationship of Venetoclax in R/R CLL and Non-Hodgkin's Lymphoma (NHL) Subjects' was included. The objective of this study was to characterise the relationship between venetoclax exposures and efficacy in R/R CLL/small lymphocytic lymphoma (SLL) subjects, as well as safety in R/R CLL/SLL and NHL subjects. Nonlinear mixed-effects population pharmacokinetic/pharmacodynamic models were developed to separately characterise the exposure-efficacy relationship between venetoclax concentrations and total circulating lymphocytes and tumour size in CLL/SLL subjects.

5.1.1. Study R&D/15/0255: Exposure-Efficacy Relationship of Venetoclax in Subjects with Relapsed or Refractory (R/R) Chronic Lymphocytic Leukemia (CLL) and the Exposure-Safety Relationship of Venetoclax in R/R CLL and Non-Hodgkin's Lymphoma (NHL) Subjects

5.1.1.1. Objective

To characterise the relationship between venetoclax exposures and efficacy in R/R CLL/small lymphocytic lymphoma (SLL) subjects, as well as safety in R/R CLL/SLL and NHL subjects.

Specific objectives of the report were:

- To describe the venetoclax exposure-efficacy relationship for circulating lymphocytes and tumour size in R/R CLL/SLL subjects.
- To characterise the relationship between venetoclax exposure and objective responses (OR) and complete remission (CR)/complete remission with incomplete marrow recovery (CRi) in R/R CLL/SLL subjects.
- To characterise the relationship between venetoclax exposure and the adverse events of neutropenia and infection in R/R CLL/SLL and NHL subjects.

Study Subjects

All CLL/SLL subjects enrolled in Studies M12-175 (Arm A only), M13-365, and M13-982 (main cohort only) who received venetoclax and had at least one measureable response (lymphocyte, tumour size measurement, and/or tumour response assessment [for example, partial remission {PR}, CRi, etc.]) by the respective enrolment (as applicable) and data cut off dates were included in the exposure-efficacy analyses. All CLL/SLL subjects described in these 3 studies, plus the NHL subjects in Study M12-175 (Arm B), the safety expansion cohort in Study M13-982, and all the subjects enrolled in Study M14-032 by the respective enrolment (as applicable) and data cut-off dates, were included for the exposure-safety analyses. In total, 272 and 444 subjects were included in the exposure-efficacy and exposure-safety analyses, respectively.

5.1.1.2. Pharmacodynamics

Indirect response models with stimulation of output adequately described both the circulating lymphocyte and tumour size responses to plasma venetoclax concentrations. The models were parameterised in terms of the baseline initial condition (R_0), the linear venetoclax effect (E_{slope}), and the first-order response output rate constant (k_{out}). Steady-state initial conditions were assumed. A constant minimum lymphocyte parameter (*MinLym*) was also incorporated into the lymphocyte pharmacokinetic/pharmacodynamic model to account for a lymphocyte sub-population unaffected by venetoclax. Inter-individual variability (IIV) was modelled using a full variance-covariance matrix with IIV terms on R_0, E_{slope}, k_{out}, and *MinLym* for the lymphocyte model and a diagonal variance-covariance matrix with IIV terms on R_0, E_{slope}, and k_{out} for the tumour size model. Residual error was described by exponential and proportional error models for lymphocytes and tumour size, respectively.

The population E_{slope} estimates were 138 (95% CI: [66.1 – 851]) and 6.84 (95% CI: [5.24 – 7.75]) mL/µg for lymphocytes and tumour size, respectively, indicating that lymphocytes are more sensitive than tumours to the effects of venetoclax. Average steady-state venetoclax concentrations of 0.00863 and 0.146 µg/mL based on the model parameter estimates in typical subjects decrease lymphocytes and tumour size by 50%, respectively. The half-life of CLL cells based on the population k_{out} estimate was 204 (95% CI: [93.5 – 1359]) days.

No covariates were incorporated into the lymphocyte model, indicating that the evaluated covariates were not influential in describing the inter-individual variability in lymphocyte response. Bodyweight was identified to have an impact on the baseline tumour size, with heavier subjects having a larger baseline tumour size. The 17p deletion somatic mutation was not identified to influence the responsiveness of lymphocytes or tumour size to venetoclax.

The logistic regression analyses of the adverse events (Grade > /= 3) of neutropenia and infection both indicated that higher average venetoclax concentrations were associated with a decrease in adverse events. Sensitivity analyses supported that increasing venetoclax concentration did not increase these adverse events and further indicated that the association may be driven by disease treatment and not by directly affecting neutrophils or granulocyte progenitor cells. Granulocyte colony stimulating factor was identified as a covariate associated with neutropenia adverse events. No other covariates were identified to be associated with neutropenia or infection adverse event (Grade > /= 3) rates.

5.2. Summary of pharmacodynamics

Higher venetoclax concentrations led to a more rapid decrease in lymphocyte counts and tumour size. Subjects with the 17p deletion chromosomal aberration appeared to be as sensitive to the effects of venetoclax as subjects who did not have the 17p deletion.

5.3. Evaluator's overall conclusions on pharmacodynamics

A venetoclax dosage of 400 mg QD maximised (> 80%) the probability of a typical subject with CLL/SLL achieving an objective response after 6-months of therapy, supporting 400 mg QD venetoclax as an appropriate dosage regimen in R/R CLL/SLL subjects. Minimal reduction (< 5%) in the ORR was predicted even with a 0.5-fold decrease in the standard exposure achieved at the 400 mg QD dosage regimen. Higher venetoclax concentrations were also not associated with an increased probability of the adverse events (Grade > /= 3) of neutropenia and infection, indicating that these evaluated safety endpoints are not dose-limiting. As such, a 0.5- to 2.0-fold change in exposure from that achieved in a typical subject at the 400 mg QD dosage regimen has minimal impact on both the ORR and the safety endpoints of neutropenia and infection.

6. Dosage selection for the pivotal studies

6.1. Pivotal Study M13-982

The dose of 400 mg was selected on the basis of preliminary data in relapsed/refractory CLL/SLL subjects from the ongoing venetoclax first-in-human Study M12-175. In this study efficacy was evaluated in 56 CLL/SLL subjects across 8 dose escalation cohorts (150 mg to 1200 mg) and in 60 subjects in a 400 mg safety expansion cohort. Anti- tumour activity was observed with venetoclax monotherapy in this study population of heavily pre-treated CLL/SLL subjects with relapsed or refractory disease, including those with high risk features (17p deletion, fludarabine-refractory, IGVH unmutated, and *TP53* mutation without 17 p deletion). Consistent, high response rates were observed across the dose cohorts and subpopulations. Initial responses were observed early with a median time to PR of 1.4 months. Deeper responses were observed with longer time on treatment; median time to CR/CRi in the dose escalation cohorts was 5.6 months with a range of 2.8 to 19.4 months. More favourable findings were observed in dose cohorts treated with venetoclax 400 mg daily or higher, as compared with cohorts treated with a daily dose less than 400 mg. Durable response at 12 months was estimated for the majority of subjects. IRC assessment of disease progression and tumour response for 57 CLL subjects treated at 400 mg at the time of the interim analysis generally confirmed the findings of the overall best response based on investigators' assessments. There were some discordance between the number of investigator-determined and IRC assessed CR/CRi.

The RPTD for CLL/SLL subjects, and hence the dose for the CLL/SLL safety expansion cohort, was determined to be 400 mg based on data from all CLL/SLL subjects in the dose escalation cohorts The safety expansion experience confirmed the safety profile demonstrated during dose escalation and confirmed that 400 mg is an appropriate RPTD for CLL/SLL.

TLS, an adverse finding with venetoclax, is also evidence of its efficacy. In M12-175, 8 of 116 CLL/SLL subjects had TLS reported as an adverse event. Of the 8 CLL/SLL subjects, only 1 had an event of TLS (laboratory) after implementation of an amendment to introduce TLS prophylaxis and management measures. When CLL/SLL subjects were reviewed, including those with high risk for TLS (that is, ALC ≥ 25 × 10^9/L plus lymph node with diameter ≥ 5, or lymph node ≥ 10 cm), the M12-175 study demonstrated that TLS is manageable with appropriate prophylaxis and monitoring. The risk of TLS was addressed by dose titration and a prophylactic regimen of hydration and uric acid reducers, along with laboratory monitoring, these activities provided adequate protection.

7. Clinical efficacy

7.1. Studies for venetoclax

for the treatment of patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy; this includes patients with 17p deletion.

7.1.1. Pivotal efficacy study

7.1.1.1. Study M13-982

A Phase II Open-Label Study of the Efficacy of ABT-199 (GDC-0199) in Subjects with Relapsed/Refractory or Previously Untreated Chronic Lymphocytic Leukaemia harbouring the 17p Deletion.

Study design, objectives, locations and dates

Preliminary data from the ongoing venetoclax first-in-human Phase I study (Study M12-175) evaluating subjects with CLL/small lymphocytic lymphoma (SLL) and NHL have indicated that venetoclax may be beneficial in subjects with relapsed CLL harbouring the 17p deletion and showed a favourable risk/benefit profile, providing support for initiating Phase II trials. M13-982 was the first Phase II study for venetoclax monotherapy in subjects with CLL, and focused on relapsed/refractory and previously untreated subjects harbouring the 17p deletion.

Main Cohort

Primary Objectives

The primary objective of the main cohort was to evaluate the efficacy of venetoclax monotherapy in subjects with relapsed or refractory CLL harbouring the 17p deletion. Efficacy was measured by ORR.

Secondary objectives

The secondary objectives were to:

- Evaluate the CR rate, PR rate, DOR, PFS, EFS, time to progression (TTP), time to first response, time to 50% reduction in ALC, OS, and percent of subjects who moved on to stem cell transplant.
- Evaluate the safety and tolerability of venetoclax in subjects with relapsed or refractory CLL harbouring the 17p deletion.

Safety Expansion Cohort

Primary Objectives

The primary objective of the safety expansion cohort was to evaluate the safety of venetoclax in approximately 50 subjects with relapsed/refractory or previously untreated CLL harbouring the 17p deletion treated per the updated TLS prophylaxis and management measures.

Secondary objectives

The secondary objectives were to evaluate ORR, CR rate, PR rate, DOR, PFS, EFS, TTP, time to first response, time to 50% reduction in ALC, OS and percent of subjects who proceeded to stem cell transplant.

Exploratory Objectives

Exploratory objectives were evaluated in both cohorts. They included:

- time to next anti-CLL treatment (TTNT)

- MRD assessed in the peripheral blood and/or bone marrow
- evaluation of PK, PG, and biomarkers
- Health Economic and Patient-Reported Outcome Measures included
- the MD Anderson Symptom Inventory (MDASI) (measure of subject reported symptoms)
- the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and EORTC Quality of Life Questionnaire-Chronic Lymphocytic Leukaemia 16 (QLQ-CLL16); a measure of health-related quality of life [QoL] specific to CLL)
- the European Quality of Life 5 Dimensions-5 Levels Questionnaire (EQ-5D-5L; a measure of general health status)
- the European Quality of Life 5 Dimensions Visual Analogue Scale (EQ VAS; also a measure of general health status)

Overall Study Design and Plan

This was an open-label, single arm, multicentre, global study to determine the efficacy of venetoclax monotherapy in subjects with relapsed/refractory or previously untreated CLL harbouring the 17p deletion. The study was designed to enrol, in the main cohort, approximately 100 subjects with relapsed or refractory CLL harbouring the 17p deletion (as confirmed by the central laboratory) and, in the safety expansion cohort, approximately 50 subjects with relapsed/refractory or previously untreated CLL harbouring the 17p deletion (as confirmed by local or central laboratory), to meet scientific and regulatory objectives.

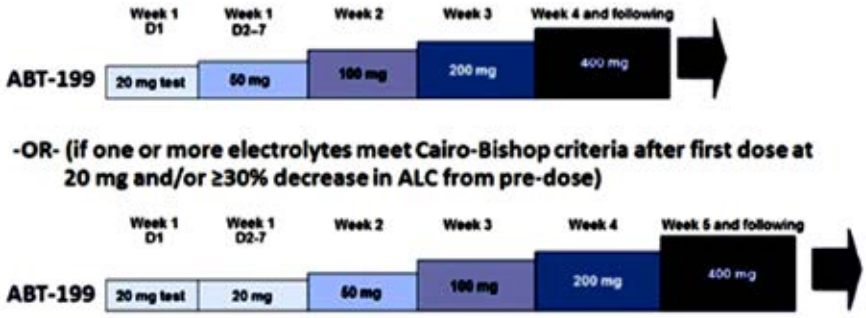
The detection of 17p13 deletion (17p del) was determined by the local laboratory and/or by the central laboratory, which used the Vysis CLL FISH probe kit. Screening must have been performed within 28 days of study drug administration. A CT scan must have been performed within 35 days prior to study drug administration. A bone marrow biopsy and aspirate was also performed at Screening (within 35 days prior to study drug administration) and again in coordination with CT scans, to confirm complete remission. Study visits were conducted on Days 1 and 2 of each week through Week 5, then on Day 1 of every 4 weeks thereafter, beginning with Week 8 until Week 36, and then Day 1 of every 12 weeks thereafter.

Main Cohort Dosing Schedule

Venetoclax was administered orally QD, continuously. Each dose of venetoclax was to be taken with approximately 240 mL of water within 30 minutes after the completion of breakfast or the subject's first meal of the day. To mitigate the risk for TLS, a Lead-In Period (up to 5 weeks) was employed to evaluate a step-wise dose escalation. All subjects were admitted to the hospital and began the Lead-In Period with an initial test dose of 20 mg venetoclax on Week 1 Day 1. If no significant findings occurred within 24 h, then a test dose of 50 mg was administered on Week 1 Day 2 followed by 50 mg venetoclax QD for 5 days (Week 1 Day 3 through Day 7). If significant findings occurred within 24 h of the initial test dose of 20 mg venetoclax on Week 1 Day 1, the 20 mg dose was maintained for 1 week prior to dose escalation to 50 mg on Week 2 Days 1 to 7.

After a week at 50 mg, the dose escalation proceeded with weekly increases in dose, as tolerated (Figure 11). A lower starting dose and/or modification to the lead-in regimen may have been implemented for individual subjects at particularly high risk for TLS.

Figure 11. Study Schema for Main Cohort

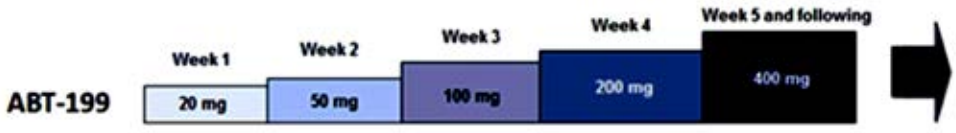


ABT-199 = venetoclax; ALC = absolute lymphocyte count; D1 = Day 1; D2 – 7 = Days 2 to 7

Safety Expansion Cohort Dosing Schedule

Venetoclax was administered orally QD, continuously. Each dose of venetoclax was to be taken with approximately 240 mL of water within 30 minutes after the completion of breakfast or the subject's first meal of the day. To mitigate the risk for TLS (evaluated by the Howard criteria[1], a Lead-In Period of 5 weeks was employed with a stepwise dose escalation (Figure 12).

Figure 12. Safety Expansion Cohort Dosing Schedule



ABT-199 = venetoclax

Inclusion and exclusion criteria

Main Inclusion

A subject was eligible for study participation if he/she met the following criteria:

- Subject voluntarily signed and dated an informed consent, approved by an IEC/IRB, prior to the initiation of any screening or study specific procedures.
- Subject was ≥ 18 years of age.
- Subject had a diagnosis of CLL that met published 2008 Modified Guidelines from the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) NCI-WG.
- Subject had an indication for treatment according to the 2008 Modified IWCLL NCI-WG Guidelines.

[1] Howard Definition of Laboratory Tumour Lysis Syndrome. This definition comprises ≥ 2 of the following metabolic abnormalities.

Element	Value
Uric Acid	≥ 476 µmol/L or 8 mg/dL
Potassium	≥ 6.0 mmol/L or 6 mEq/L
Inorganic Phosphorus	≥ 1.45 mmol/L
Calcium	≤ 1.75 mmol/L

- Subject had clinically measurable disease (defined in the safety expansion cohort as lymphocytosis > 5 × 109 cells/L and/or palpable and measurable nodes by physical exam and/or organomegaly assessed by physical exam).
- Subject had to have relapsed/refractory CLL or previously untreated CLL (safety expansion cohort)

Relapsed or refractory CLL subjects had to meet the following requirements:

- Refractory or had relapsed after receiving at least 1 prior line of therapy (subjects that progressed after 1 cycle of treatment [safety expansion cohort] or had completed at least 2 cycles of treatment for a given line of therapy.

Previously untreated CLL subjects had to meet the following requirements:

- Received no prior chemotherapy or immunotherapy. Subjects with a history of emergency loco-regional radiotherapy (for example, for relief of compressive signs or symptoms) were eligible.
- CLL diagnostic criteria above, and subjects had to have > 5 × 109 cells/L B-lymphocytes in the peripheral blood.
- Subject had the 17p deletion, assessed by:
    a. Main cohort: central laboratory (peripheral blood), and determined by FISH using the Vysis CLL probe kit.
    b. Safety expansion cohort: local laboratory (in bone marrow or peripheral blood) or assessed by central laboratory (peripheral blood). A result obtained prior to study Screening could be used for eligibility. Additionally, a confirmatory sample (peripheral blood) was sent to the central laboratory; however, these results did not impact participation in the study.
- Subject had an Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 2.
- Subject had adequate bone marrow function at Screening as follows:
    a. Absolute neutrophil count (ANC) ≥ 1000/μL, or:
        i. Main cohort: For subjects who had an ANC< 1000/μL at Screening and bone marrow heavily infiltrated with underlying disease (approximately 80% or more), granulocyte-colony stimulating factor (G-CSF) may have been administered after Screening and prior to the first dose of venetoclax to achieve the ANC eligibility criteria (≥ 1000/μL).
        ii. Safety expansion cohort: For subjects who had an ANC < 1000/μL at Screening and bone marrow heavily infiltrated with underlying disease (unless cytopenia was clearly due to marrow involvement of CLL), growth factor support could have been administered after Screening and prior to the first dose of venetoclax to achieve the ANC eligibility criteria (≥ 1000/μL).
    b. Platelets:
        i. Main cohort: > 40,000/mm^3 (entry platelet count had to be independent of transfusion within 14 days of Screening).
        ii. Safety expansion cohort:

            Platelets ≥ 30,000/mm^3,

            Without transfusion support within 14 days of Screening,

            Without evidence of mucosal bleeding,

Without known history of bleeding episode within 3 months of Screening

Without history of bleeding disorder

c. Haemoglobin ≥ 8.0 g/dL.

· Subject had adequate coagulation, renal, and hepatic function per laboratory reference ranges at Screening as follows:

a. Activated partial thromboplastin time (aPTT) and prothrombin time (PT) not to exceed 1.5 × the upper limit of normal (ULN)

b. Calculated creatinine clearance > 50 mL/min using 24-h creatinine clearance or modified Cockcroft-Gault equation (estimated creatinine clearance rate using Cockcroft-Gault formula [eCCr]; using ideal body mass [IBM] instead of mass)

c. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 × the ULN of institution's normal range; bilirubin ≤ 1.5 × ULN.

· Female subjects of childbearing potential and non-sterile male subjects must have practiced at least 1 of the following methods of birth control with partner(s) beginning with initial study drug administration and continuing to 30 days after the last dose of study drug:

a. Total abstinence from sexual intercourse as the preferred life style of the subject; periodic abstinence was not acceptable.

b. Surgically sterile partner(s); acceptable sterility surgeries were: vasectomy, bilateral tubal ligation, bilateral oophorectomy or hysterectomy.

c. Intrauterine device.

d. Double-barrier method (contraceptive sponge, diaphragm, or cervical cap with spermicidal jellies or cream AND a condom).

e. Hormonal contraceptives (oral, parenteral, or transdermal) for at least 3 months prior to study drug administration.

f. If hormonal contraceptives were used, the specific contraceptive had to have been used for at least 3 months prior to study drug administration. If the subject was currently using a hormonal contraceptive, she was also to use a barrier method during this study from initial study drug administration to 90 days (30 days as of Protocol Amendment 2) after the last dose of study drug. Any contraception method was to be continued for 90 days (30 days as of Protocol Amendment 2) after the last dose of study drug.

· Females of childbearing potential (that is, not postmenopausal for at least 1 year with no alternative medical reason or surgically sterile) had negative results for pregnancy test performed:

a. At Screening with a serum sample obtained within 14 days prior to the first study drug administration.

b. Prior to dosing with a urine sample obtained on Week 1 Day 1 (tested locally), if it had been > 7 days since obtaining the serum pregnancy test results.

· Male subjects agreed to refrain from sperm donation from initial study drug administration until 90 days after the last dose of study drug.

· For high risk subjects (high risk of TLS) a pre-approval by the AbbVie medical monitor was required prior to enrolment.

Exclusion: A patient was not eligible for participation in this study if any of the following criteria applied:

- Subject had undergone an allogeneic stem cell transplant.
- Subject had developed Richter's transformation.
- Subject had prolymphocytic leukaemia (safety expansion cohort only).
- Subject had active and uncontrolled autoimmune cytopenias:
- Protocol Amendment 1 (main cohort): for 2 weeks, including autoimmune hemolytic anaemia (AIHA) and idiopathic thrombocytopenic purpura (ITP).
- For 2 weeks prior to Screening, including AIHA and ITP despite low dose corticosteroids Starting with Protocol Amendment 2 (safety expansion cohort).
- Subject had previously received venetoclax.
- Subject was known to be positive for human immunodeficiency virus (due to potential drug-drug interactions between anti-retroviral medications and venetoclax, as well as anticipated venetoclax mechanism-based lymphopenia that may have potentially increased the risk of opportunistic infections).
- Subject had received the following within 8 weeks (main cohort) or within 30 days (safety expansion cohort) prior to the first dose of study drug:
    a. A biologic agent (that is, monoclonal antibodies) for anti-neoplastic intent.
- Subject had received any of the following within 14 days (main cohort) or within 5 half-lives (safety expansion cohort) or within 14 days or 5 half-lives (safety expansion cohort), as applicable, prior to the first dose of study drug, or had not recovered to less than National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade 2 clinically significant adverse effect(s)/toxicity(s) of the previous therapy:
    a. Any anticancer therapy including chemotherapy, or radiotherapy.
    b. Investigational therapy, including targeted small molecule agents.
- Subject had received the following within 7 days prior to the first dose of study drug:
    a. Steroid therapy for anti-neoplastic intent.
    b. Cytochrome P450 (CYP) 3A inhibitors (such as fluconazole, ketoconazole, and clarithromycin).
    c. Potent CYP3A inducers (for example, rifampin, phenytoin, carbamazepine, or St. John's Wort).
    d. Warfarin, or required the use of warfarin (due to potential drug-drug interactions that may have potentially increased the exposure of warfarin and complications of this effect).
    e. Antiretroviral medications (main cohort only).
- Subject had consumed the following within 3 days prior to the first dose of study drug.
    a. Grapefruit or grapefruit products.
    b. Seville oranges (including marmalade-containing Seville oranges).
    c. Star fruit.
- Subject had a known allergy to both xanthine oxidase inhibitors and rasburicase.
- Subject had a cardiovascular disability status of New York Heart Association Class ≥ 2. Class 2 is defined as cardiac disease in which subjects are comfortable at rest but ordinary physical activity, results in fatigue, palpitations, dyspnea, or anginal pain.

- Subject exhibited evidence of other clinically significant uncontrolled condition(s) including, but not limited to:
  a. Main cohort: uncontrolled systemic infection (viral, bacterial, or fungal).
  b. Safety expansion cohort:
     i. Uncontrolled and/or active systemic infection (viral, bacterial, or fungal).
     ii. Chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) requiring treatment.
     iii. Febrile neutropenia.
  - Subject had a significant history of renal, pulmonary, neurologic, psychiatric, endocrinologic, metabolic, immunologic, cardiovascular, or hepatic disease that in the opinion of the investigator would have adversely affected his/her participating in this study. For subjects who required an intervention for any above diseases within the past 6 months, correspondence with the investigator and the AbbVie medical monitor had to occur.
- A female subject was pregnant or breastfeeding.
- Subject had a history of active malignancies other than CLL within the past 2 years prior to study entry, with the exception of:
  a. Adequately treated in situ carcinoma of the cervix uteri.
  b. Adequately treated basal cell carcinoma or localized squamous cell carcinoma of the skin.
  c. Previous malignancy confined and surgically resected (or treated with other modalities) with curative intent.
- Subject had malabsorption syndrome or other condition that precluded enteral route of administration.

Study treatments

There were 2 treatment groups: the main cohort and the safety expansion cohort. All subjects were to be dosed at the final dose of 400 mg following a Lead-In Period to evaluate a stepwise dose escalation, as shown in Figure 11 and Figure 12.

Efficacy variables and outcomes

Assessment of Efficacy

- Primary Efficacy Analyses in Main Cohort

The primary efficacy endpoint was ORR – the proportion of subjects with an overall response (CR + CRi + nPR + PR) per the NCI-WG guidelines as assessed by the IRC in the first 70 subjects enrolled treated in the main cohort.

The ORR for venetoclax was tested to reject the null hypothesis of 40%. If the null hypothesis was rejected and the ORR was greater than 40%, then venetoclax was shown to have an ORR significantly greater than 40%. In addition, the 95% confidence interval (CI) for ORR based on binomial distribution was constructed. Per the pre specified primary efficacy analysis, the assessment of ORR was performed once 70 subjects in the main cohort had completed the scheduled 36-week disease assessment, had progressed prior to the 36-week disease assessment, discontinued study drug for any reason, or after all treated subjects had discontinued venetoclax, whichever was earlier. Among these 70 subjects, those who had not achieved a CR, CRi, nPR, or confirmed PR prior to the data cut-off date were considered to be non-responders. Per the recommendation of the regulatory agencies, the timing of the efficacy

analysis for the main cohort was modified to occur after 107 subjects had completed the 36-week disease assessment.

· Secondary Efficacy Analyses in the Main Cohort

Secondary efficacy endpoints included CR rate, PR rate, DOR, PFS, EFS, TTP, time to response, time to 50% reduction in ALC, OS, and percent of subjects who moved on to stem cell transplant.

· Supplemental Efficacy in the Main Cohort

A supplemental assessment of efficacy occurred when the last subject enrolled in the main cohort completed the 36-week disease assessment. This assessment was based on the IRC assessment for all treated subjects in the main cohort.

The following analyses were provided: ORR, CR rate, PR rate, DOR, PFS, EFS, TTP, time to response, time to 50% reduction in ALC, and MRD response rate. The analyses were performed as described above. Confidence intervals were presented for each analysis. No statistical tests were performed on the supplemental assessments of efficacy.

· Additional Exploratory Efficacy Analyses

The TTNT was defined as the number of days from the date of the first dose of venetoclax to the date of first dose of new non-protocol anti-lymphoma therapy (NPT) or death from any cause. For subjects who did not take NPT, the data were censored at the last known date to be free of NPT. The TTNT was analysed by Kaplan-Meier methodology using data for all treated subjects. Median TTNT time was calculated and the 95% CI for median TTNT time was presented.

The rate of MRD negativity in subjects was an exploratory endpoint. This rate as defined as the proportion of subjects who had MRD negativity status. The 95% CIs based on the binomial distribution were provided.

Health Economic and Patient Reported Outcome measures included the MDASI, EORTC QLQ-C30 and QLQ-CLL16, EQ-5D-5L, and EQ VAS. Descriptive statistics were calculated for all scales of the MDASI, EORTC QLQ-C30, and EORTC QLQ-CLL16, EQ-5D-5L utility score, and EQ VAS score, including mean change from Baseline to each assessment as well as the Final Visit. Additionally, the EORTC QLQ-C30 and EORTC QLQ-CLL16 were to be administered through post-treatment. The results obtained for each instrument was explored for trends and summarized as appropriate.

A sensitivity analysis of ORR, CR rate, PR rate, DOR, PFS, and TTP based on the investigator assessment was performed using the primary subjects analysis set (first 70 subjects treated) and all 107 subjects treated in the main cohort.

· Safety expansion cohort

For this interim report, efficacy was not assessed in the safety expansion cohort due to the limited duration of treatment in this cohort. All efficacy analyses for the safety expansion cohort will be presented in the final report for this study.

Definitions of Treatment Response

The CR rate was defined as the proportion of subjects who achieved a CR or CRi per the NCI-WG criteria (determined by the IRC in the main cohort). In addition, the 95% CI based on the binomial distribution was provided. Subjects who did not achieve a CR or CRi were considered to be non-responders in the calculation of CR rate.

The PR rate was defined as the proportion of subjects who achieved an nPR or PR per the NCI-WG criteria (determined by the IRC in the main cohort). In addition, the 95% CI based on the binomial distribution was provided. Subjects who did not achieve an nPR or PR were considered to be non-responders in the calculation of PR rate.

The DOR was defined as the number of days from the date of first response (CR, CRi, nPR or PR; determined by the IRC in the main cohort) to the earliest recurrence of progressive disease per the IRC assessment. If a subject was still responding, then the subject's data were censored at the date of the subject's last available disease assessment. For subjects who never experienced a response, the subject's data were not included in the analysis. The DOR was analysed by Kaplan-Meier methodology. Median DOR was calculated and the corresponding 95% CI was presented.

Duration of PFS was defined as the number of days from the date of first dose to the date of earliest disease progression (determined by the IRC in the main cohort) or death. All disease progression was included regardless whether the event occurred while the subject was taking the study drug or had previously discontinued the study drug. If the subject did not experience disease progression or death, then the data were censored at the date of last disease assessment. Data for subjects who received non-protocol anti-CLL therapy prior to disease progression were censored at the last disease assessment prior to receiving non-protocol therapy. Data for subjects without any disease assessments performed after the Baseline Visit were censored at the time of enrolment plus 1 day. Progression -free survival was analysed by Kaplan-Meier methodology. Median time of PFS was calculated and the 95% CI for median time of PFS was presented.

Event-free survival was defined as the number of days from the date of first dose to the date of earliest disease progression, death, or start of a new anti-leukemic therapy. If the specified event (disease progression, death, start of a new anti-leukemic treatment) did not occur, patients were censored at the date of last disease assessment. Data for subjects without any disease assessments performed after the Baseline Visit were censored at the date of first dose plus 1 day. Event-free survival was analysed by Kaplan-Meier methodology. Event-free survival was calculated and the 95% CI for median EFS was presented.

The TTP was defined as the number of days from the date of first dose to the date of earliest disease progression (determined by the IRC in the main cohort). All disease progression was included regardless whether the event occurred while the subject was taking the study drug or had previously discontinued the study drug. If the subject did not experience disease progression, then the data were censored at the date of last available disease assessment. Data for subjects who received non-protocol CLL therapy prior to disease progression were censored at the last disease assessment prior to receiving non-protocol therapy. Data for subjects without any disease assessments performed after the baseline visit were censored at the time of enrolment plus 1 day. The TTP was analysed by Kaplan-Meier methodology. Median TTP was calculated and the 95% CI for median TTP was presented.

Time to first response was defined as the number of days from the date of first dose to the date of the first sign of response (CR, CRi, nPR, or PR) given the subject has had a CR, CRi, confirmed nPR, or confirmed PR per the 2008 Modified IWCLL NCI-WG criteria. The first response could have been an assessment by physical examination, as long as the results were later confirmed per the NCI-WG criteria. For subjects who never experienced a response, the subject's data were not included in the analysis. Descriptive statistics (mean, SD, median, and range) and the 95% CI of the mean were presented.

Time to 50% reduction in ALC was defined as the number of days (h if applicable) from the date of first dose to the date when the ALC was reduced to 50% of the Baseline value. For subjects who never achieved a 50% reduction in ALC, the subject's data were not included in the analysis. Descriptive statistics (mean, SD, median, and range) and the 95% CI of the mean were presented.

Overall survival was defined as number of days from the date of first dose to the date of death for all dosed subjects. For subjects who did not die, their data were censored at the date of last study visit or the last known date to be alive, whichever was later. Overall survival was analysed

by Kaplan-Meier methodology. Median time survival was estimated and the 95% CI for the median time survival were presented.

Analysis populations

Subjects with relapsed or refractory CLL who harboured the 17p deletion participated in the main cohort of this study. In addition, subjects in this cohort were required to have17p deletion assessed by the central laboratory and determined by fluorescence in situ hybridization (FISH) using the Vysis CLL probe kit. Subjects had to be relapsed or refractory after receiving at least 1 prior treatment regimen.

Subjects with relapsed/refractory or previously untreated CLL who harboured the 17p deletion were selected to participate in the safety expansion cohort of this study. Subjects in this cohort were required to have the 17p deletion assessed by central laboratory. In addition, subjects in this cohort could enrol based on a 17p deletion assessed by their local laboratory. Subjects underwent Screening procedures within 21 days (main cohort) or 28 days (safety expansion cohort) prior to initial study drug administration (the exception to this was the CT scan and bone marrow biopsy and aspirate, which was completed within 28 days (main cohort) or 35 days (safety expansion cohort) prior to study drug administration). Adult male and female subjects who met the inclusion criteria and who did not meet any of the exclusion criteria were eligible for enrolment into the study.

Sample size

Approximately 100 subjects were to be enrolled in the main cohort to assess the safety and efficacy of venetoclax in subjects with relapsed or refractory CLL harbouring the 17p deletion. With this sample size, if an AE occurred at a rate of 2%, then the probability of observing at least 1 event in a trial with 100 subjects was 86%. Assuming a peak enrolment rate of 0.11 subjects/site/month; it was anticipated that approximately 100 subjects would be enrolled during the 14 month enrolment phase. The primary assessment of the efficacy of venetoclax was to occur around Month 19, at which time 70 subjects would have had their 36-week disease assessment. The final efficacy summary is to occur around Month 38 (2 years after the last subject enrols). Overall response rates for CLL subjects with 17p deletion range from approximately 7% to 77%, with the higher responses in alternative, but also more toxic, regimens such as alemtuzumab + steroids. Conventional therapies such as FCR and BR demonstrated ORRs of 35% and 7%, respectively. Therefore, a therapy providing significant benefit in ORR over a standard rate of 40% was to be considered clinically meaningful.

Performing the efficacy analyses at 70 subjects provided at least 90% power (at 2-sided alpha of 5%) to reject the null hypothesis of 40% ORR in favour of an alternative hypothesis of 60% ORR. The power calculations for a range of different sample sizes are presented in Table 13.

Table 13. Sample Size Calculation

Subjects (N)	Power (%)
50	76
60	82
70	90
80	93
90	96

For the safety expansion cohort, an additional 50 subjects with relapsed/refractory or previously untreated CLL harbouring the 17p deletion were to be enrolled to assess the modifications made to the initial dosing of venetoclax for the management of TLS. With this

sample size, if a TLS event occurred at a rate of 2%, then the probability of observing at least 1 event in this cohort of 50 subjects was 64%.

Statistical methods

Efficacy analyses were performed for all subjects in the main cohort only. Safety analyses were performed on all subjects who received at least 1 dose of venetoclax in the main cohort, unless otherwise specified. For the primary efficacy analyses, statistical significance was determined by a 2-sided P value < 0.05 (1-sided < 0.025).

Baseline Characteristics

All Baseline summary statistics were based on characteristics prior to the initiation of study drug. Unless otherwise stated, Baseline for a given variable was defined as the last value for that variable obtained prior to the first dose of study drug.

Demographics

Descriptive statistics were provided for Baseline demographic variables. Age, height, and weight were summarized with means, medians, standard errors (SEs), SDs, and ranges. Frequencies and percentages were provided for gender and race.

Medical History

Frequencies and percentages were summarized for each medical history parameter.

Primary Efficacy Analyses in Main Cohort

The primary efficacy endpoint was ORR; the proportion of subjects with an overall response (CR + CRi + nPR + PR) per the NCI-WG guidelines as assessed by the IRC in the first 70 subjects enrolled treated in the main cohort.

The ORR for venetoclax was tested to reject the null hypothesis of 40%. If the null hypothesis was rejected and the ORR was greater than 40%, then venetoclax was shown to have an ORR significantly greater than 40%. In addition, the 95% confidence interval (CI) for ORR based on binomial distribution was constructed.

Per the pre-specified primary efficacy analysis, the assessment of ORR was performed once 70 subjects in the main cohort had completed the scheduled 36-week disease assessment, had progressed prior to the 36-week disease assessment, discontinued study drug for any reason, or after all treated subjects had discontinued venetoclax, whichever was earlier. Among these 70 subjects, those who had not achieved a CR, CRi, nPR or confirmed PR prior to the data cut-off date were considered to be non-responders. As per the recommendation of the regulatory agencies, the timing of the efficacy analysis for the main cohort was modified to occur after 107 subjects had completed the 36-week disease assessment.

Secondary Efficacy Analyses in the Main Cohort

Secondary efficacy endpoints included CR rate, PR rate, DOR, PFS, EFS, TTP, time to response, time to 50% reduction in ALC, OS, and percent of subjects who moved on to stem cell transplant. The CR rate was defined as the proportion of subjects who achieved a CR or CRi per the NCI-WG criteria (determined by the IRC in the main cohort). In addition, the 95% CI based on the binomial distribution was provided. Subjects who did not achieve a CR or CRi were considered to be non-responders in the calculation of CR rate.

The PR rate was defined as the proportion of subjects who achieved an nPR or PR per the NCI-WG criteria (determined by the IRC in the main cohort). In addition, the 95% CI based on the binomial distribution was provided. Subjects who did not achieve an nPR or PR were considered to be non-responders in the calculation of PR rate.

The DOR was defined as the number of days from the date of first response (CR, CRi, nPR or PR; determined by the IRC in the main cohort) to the earliest recurrence of progressive disease per the IRC assessment. If a subject was still responding, then the subject's data were censored at

the date of the subject's last available disease assessment. For subjects who never experienced a response, the subject's data were not included in the analysis. The DOR was analysed by Kaplan-Meier methodology. Median DOR was calculated and the corresponding 95% CI was presented.

Duration of PFS was defined as the number of days from the date of first dose to the date of earliest disease progression (determined by the IRC in the main cohort) or death. All disease progression was included regardless whether the event occurred while the subject was taking the study drug or had previously discontinued the study drug. If the subject did not experience disease progression or death, then the data were censored at the date of last disease assessment. Data for subjects who received non-protocol anti-CLL therapy prior to disease progression were censored at the last disease assessment prior to receiving non-protocol therapy. Data for subjects without any disease assessments performed after the Baseline Visit were censored at the time of enrolment plus 1 day. Progression -free survival was analysed by Kaplan-Meier methodology. Median time of PFS was calculated and the 95% CI for median time of PFS was presented.

Event-free survival was defined as the number of days from the date of first dose to the date of earliest disease progression, death, or start of a new anti-leukemic therapy. If the specified event (disease progression, death, start of a new anti-leukemic treatment) did not occur, patients were censored at the date of last disease assessment. Data for subjects without any disease assessments performed after the Baseline Visit were censored at the date of first dose plus 1 day. Event-free survival was analysed by Kaplan-Meier methodology. Event-free survival was calculated and the 95% CI for median EFS was presented.

The TTP was defined as the number of days from the date of first dose to the date of earliest disease progression (determined by the IRC in the main cohort). All disease progression was included regardless of whether the event occurred while the subject was taking the study drug or had previously discontinued the study drug. If the subject did not experience disease progression, then the data were censored at the date of last available disease assessment. Data for subjects who received non-protocol CLL therapy prior to disease progression were censored at the last disease assessment prior to receiving non-protocol therapy. Data for subjects without any disease assessments performed after the baseline visit were censored at the time of enrolment plus 1 day. The TTP was analysed by Kaplan-Meier methodology. Median TTP was calculated and the 95% CI for median TTP was presented.

Time to first response was defined as the number of days from the date of first dose to the date of the first sign of response (CR, CRi, nPR, or PR) given the subject has had a CR, CRi, confirmed nPR, or confirmed PR per the 2008 Modified IWCLL NCI-WG criteria. The first response could have been an assessment by physical examination, as long as the results were later confirmed per the NCI-WG criteria. For subjects who never experienced a response, the subject's data were not included in the analysis. Descriptive statistics (mean, SD, median, and range) and the 95% CI of the mean were presented.

Time to 50% reduction in ALC was defined as the number of days (h if applicable) from the date of first dose to the date when the ALC was reduced to 50% of the Baseline value. For subjects who never achieved a 50% reduction in ALC, the subject's data were not included in the analysis. Descriptive statistics (mean, SD, median, and range) and the 95% CI of the mean were presented.

Overall survival was defined as number of days from the date of first dose to the date of death for all dosed subjects. For subjects who did not die, their data were censored at the date of last study visit or the last known date to be alive, whichever was later. Overall survival was analysed by Kaplan-Meier methodology. Median time survival was estimated and the 95% CI for the median time survival were presented.

The percent of subjects who moved on to stem cell transplant were summarised and the 95% CI based on the binomial distribution was provided.

Timing of Efficacy and Safety Analyses

The date once 70 subjects in the main cohort completed the scheduled 36-week disease assessment, progressed prior to the 36-week disease assessment, discontinued study drug for any reason, or after all enrolled subjects discontinued venetoclax, whichever was earlier, was defined as the data 'cut-off' date for the primary efficacy analyses (ORR, CR rate, PR rate, DOR, PFS, TTP, OS, and additional exploratory efficacy analyses). Efficacy data (IRC assessment of first 70 subjects treated in the main cohort and investigators' assessment on all treated subjects in the main cohort) and safety data (all treated subjects in the main cohort) up to and including this date were collected. The exact data cut-off date for all efficacy and safety analyses was detailed in a SAP, which was signed-off prior to the data cut-off date. During this data collection period, active subjects continued to receive venetoclax, as applicable. When data collection was complete and all data management QA and QC procedures were performed, the clinical database data were extracted for documentation and statistical analyses.

As per the recommendation of the regulatory agencies, the timing of the efficacy analysis for the main cohort was modified to occur after 107 subjects had completed the 36-week disease assessment. Therefore, results are presented in this interim report for IRC-assessed ORR for the first 70 subjects and the 107 subjects in the main cohort. In addition, results are presented for investigator-assessed ORR for the 107 subjects in the main cohort.

When all subjects treated into the main cohort have completed the scheduled 36-week disease assessment, experienced disease progression prior to the 36-week disease assessment, or discontinued study drug for any reason, additional supplemental efficacy assessments based on the IRC review of response will be performed. Any active subjects will continue to receive venetoclax until they discontinue or for up to 2 years from the date the last subject enrols in the study.

Once the last enrolled subject discontinues/completes the cohort, the cohort will be considered complete and all remaining data will be collected and entered into the clinical database. A final efficacy assessment based on investigator assessment (ORR, CR rate, PR rate, DOR, PFS, TTP, OS, and additional exploratory efficacy analyses) will be performed once all subjects from the main cohort have completed/discontinued. No statistical tests will be performed; only descriptive statistics and the 95% CIs will be presented.

Overall survival will be collected on all subjects for up to 5 years from when the last subject enrolled in the cohort. After all survival data have been collected and entered into the clinical database, a final analysis will be performed on this dataset.

Participant flow

Fifty-six investigative sites were approved to receive study drug supplies on behalf of AbbVie and screen and enrol subjects in the study. As of the data cut-off date (30 April 2015), subjects were enrolled at 38 investigative sites globally, including sites in Australia, Canada, France, Germany, Poland, United Kingdom, and USA.

A total of 151 subjects were enrolled in the study as of the data cut-off date for this interim report (30 April 2015). Of the 151 subjects enrolled in the study, 145 subjects started treatment prior to (or on) 26 March 2015 and therefore had the opportunity to complete the 5-week lead-in period and were evaluable for the purposes of this report, including all 107 subjects in the main cohort and 38/50 subjects in the safety expansion cohort (Table 14). In the main cohort, 104 subjects achieved the target dose of 400 mg, and 3 subjects discontinued venetoclax prior to completing the lead-in period. In the safety expansion cohort, 36 subjects achieved the target dose of 400 mg. One subject discontinued prior to achieving the target dose of 400 mg and 1 subject was still in the lead-in period at the time of the data cut-off date of this report.

A total of 107 subjects (73.8%) were enrolled in the main cohort, 36 subjects (24.8%) were enrolled in the safety expansion cohort and 2 (1.4%) were enrolled in the safety expansion cohort under Protocol Amendment 3.

An additional 80 subjects were screened for enrolment into the study, but were ineligible for study participation. The reasons for the Screening failures included failure to meet the study's entrance criteria (68 subjects), lost to follow-up (1 subject), and 'other' reasons (13 subjects); note that more than 1 reason for the Screening failure may have been provided per subject.

Table 14. Disposition of Subjects

	Main Cohort (N = 107) n (%)	Safety Expansion Cohort (N = 38) n (%)	Total (N = 145) n (%)
Enrolled subjects[a]	107	38	145
Active on venetoclax at data cut-off (30 Apr 2015)	70 (65.4)	33 (86.8)	103 (71.0)
Active on study at data cut-off (30 Apr 2015)	72 (67.3)	33 (86.8)	105 (72.4)

All enrolled subjects received at least 1 dose of venetoclax

Forty-two subjects (29%) discontinued venetoclax as of the data cut-off date: 37 in the main cohort and 5 in the safety expansion cohort (Table 15). The most common reasons for venetoclax discontinuation were disease progression (13/145 subjects; 9.0%), Richter's Syndrome (11/145 subjects; 7.6%), and adverse events not related to disease progression (10/145 subjects; 6.9%).

Table 15. Primary Reasons for Discontinuation of Venetoclax – All Treated Subjects

Reason	Main Cohort (N = 107) n (%)	Safety Expansion Cohort (N = 38) n (%)	Total (N = 145) n (%)
Active on venetoclax at data cut-off (30 Apr 2015)	70 (65.4)	33 (86.8)	103 (71.0)
Discontinued venetoclax	37 (34.6)	5 (13.2)	42 (29.0)
Primary reasons[a]			
Disease progression per protocol	11 (10.3)	2 (5.3)	13 (9.0)
Progressive disease – Richter's	9 (8.4)	2 (5.3)	11 (7.6)
Adverse event related to disease progression	2 (1.9)	0	2 (1.4)
Adverse event – not related to disease	9 (8.4)	1 (2.6)	10 (6.9)

Reason	Main Cohort (N = 107) n (%)	Safety Expansion Cohort (N = 38) n (%)	Total (N = 145) n (%)
progression			
Withdrew consent	2 (1.9)	0	2 (1.4)
Stem cell transplant	3 (2.8)	0	3 (2.1)
Other[b]	1 (0.9)	0	1 (0.7)

Total does not include Subject 40011 who experienced Richter's Syndrome after the data cut-off date of 30 April 2015 and Subject 40714 who did not have Richter's Syndrome listed under 'other reason for discontinuation' and not under the primary reason for discontinuation. d=Other = noncompliance.

Major protocol violations/deviations

A summary of medically significant protocol deviations identified in the study as of the data cut-off date is presented in Table 16 (Main cohort) and Table 17 (Safety Expansion cohort).

Table 16. Summary of Protocol Deviations in the Main Cohort

	Protocol Deviation Categories – Main Cohort		
Inclusion/exclusion	1		
Prohibited concomitant medication	15		
Incorrect dose of Venetoclax	2		
Treatment compliance	6		
Failure to discontinue subjects	1		
Other Good Clinical Practices	3		
Guidelines Pertaining to TLS Prophylaxis	Medically Significant	Not Medically Significant	Total
Risk assessment not categorized appropriately	0	0	0
Dose not escalated properly	7	0	7
Uric acid reducer not administered for all doses	2	15	17
Not hospitalised when required			
High Risk	5	0	5
Medium Risk (Creatinine Clearance < 80 mL/min)	0	25	25
Intravenous hydration not administered	4	6	10
Essential chemistry panel not obtained	32	18	50
Not obtained at Baseline	4	5	9
Not obtained at 6 hrs post dose or 8 hrs post dose	24	14	38
Not obtained at 24 hrs post dose	17	9	26

Table 17. Summary of Protocol Deviations in the Safety Expansion Cohort

	Protocol Deviation Categories – Safety Expansion Cohort		
Inclusion/exclusion	0		
Prohibited concomitant medication	1		
Incorrect dose of Venetoclax	0		
Treatment compliance	0		
Failure to discontinue subjects	0		
Other Good Clinical Practices	1		
Guidelines Pertaining to TLS Prophylaxis	**Medically Significant**	**Not Medically Significant**	**Total**
Risk assessment not categorized appropriately	0	0	0
Dose not escalated properly	3	0	3
Uric acid reducer not administered for all doses	0	3	3
Not hospitalized when required			
· High Risk	0	1	1
· Medium Risk (Creatinine Clearance < 80 mL/min)	0	0	0
Intravenous hydration not administered	0	1	1
Essential chemistry panel not obtained	3	8	11
· Not obtained at Baseline	2	1	3
· Not obtained at 6 hrs post dose or 8 hrs post dose	1	7	8
· Not obtained at 24 hrs post dose	2	2	4

Baseline data

A majority of subjects were male (63.4%), and White (97.9%) (Table 18). Consistent with the expected demographics of subjects with CLL, a majority (60.0%) of subjects were ≥ 65 years of age (median 67.0 years; range 29.0 to 85.0 years); of note, 19.3% of subjects were ≥ 75 years of age. The median number of prior oncology regimens was 2 (range 1 to 10).

Table 18. Baseline Demographic Characteristics – All Treated Subjects

Category Characteristic/Statistic	Main Cohort (N = 107)	Safety Expansion Cohort (N = 38)	Total (N = 145)
Sex			
Female, n (%)	37 (34.6)	16 (42.1)	53 (36.6)
Male, n (%)	70 (65.4)	22 (57.9)	92 (63.4)
Race			

Category Characteristic/Statistic	Main Cohort (N = 107)	Safety Expansion Cohort (N = 38)	Total (N = 145)
White, n (%)	103 (97.2)	37 (100)	140 (97.9)
Black or African American, n (%)	3 (2.8)	0	3 (2.1)
Missing	1	1	2
Age (years)			
Mean (SD)	65.7 (9.87)	66.9 (10.30)	66.0 (9.96)
Median	67.0	68.0	67.0
Range	37.0 – 85.0	29.0 – 83.0	29.0 – 85.0
Number of Prior Oncology Regimens[a]			
Mean (SD)	2.9 (1.92)	2.3 (1.55)	2.8 (1.84)
Median	2.0	2.0	2.0
Range	1.0 – 10.0	1.0 – 6.0	1.0 – 10.0
1	29	-	-
2	25	-	-
3	21	-	-
4	14	-	-
≥ 5	18	-	-

Disease Stage at Diagnosis and Baseline Eastern Cooperative Oncology Score

Baseline disease characteristics are reported in Table 19. Disease stage was reported using the Rai and/or Binet staging systems. The subjects' disease stage at the time of diagnosis was reported for approximately half (70/145 subjects; 48.3%) of subjects using the Rai staging system, the Binet staging system (89/145 subjects; 61.4%), or both. Of the subjects whose disease was staged using the Rai system, a majority (52/70 subjects; 74.3%) were diagnosed as having Stage 0, Stage 1, or Stage 2 CLL. Of the subjects whose disease was staged using the Binet system, a majority (69/89 subjects; 77.5%) were diagnosed as having Stage A or Stage B CLL.

The majority of subjects enrolled in the study had an ECOG performance status of Grade 0 (60/145 subjects; 41.4%) or Grade 1 (74/145 subjects; 51.0%) at baseline. No subject had an ECOG Performance Status greater than grade 2 per the study exclusion criteria (Table 19).

Table 19. Disease Stage at Diagnosis and Baseline Eastern Cooperative Oncology Score – All Treated Subjects

Category Characteristic/Statistic	Main Cohort (N = 107)	Safety Expansion Cohort (N = 38)	Total (N = 145)
Rai Stage at Diagnosis[a]			
Stage 0	12 (25.0)	5 (22.7)	17 (24.3)
Stage 1	5 (10.4)	9 (40.9)	14 (20.0)
Stage 2	16 (33.3)	5 (22.7)	21 (30.0)

Category Characteristic/Statistic	Main Cohort (N = 107)	Safety Expansion Cohort (N = 38)	Total (N = 145)
Stage 3	3 (6.3)	1 (4.5)	4 (5.7)
Stage 4	12 (25.0)	2 (9.1)	14 (20.0)
Missing	59	16	75
Binet Stage at Diagnosis[a]			
Stage A	35 (45.5)	6 (50.0)	41 (46.1)
Stage B	24 (31.2)	4 (33.3)	28 (31.5)
Stage C	18 (23.4)	2 (16.7)	20 (22.5)
Missing	30	26	56
ECOG Performance Status			
Grade 0	42 (39.3)	18 (47.4)	60 (41.4)
Grade 1	56 (52.3)	18 (47.4)	74 (51.0)
Grade 2	9 (8.4)	2 (5.3)	11 (7.6)

ECOG = Eastern Cooperative Oncology Group. Percentages for disease stage at diagnosis were calculated using the number of non-missing values as the denominator.

Chromosomal Aberrations

All subjects enrolled in the study were to harbour the 17p deletion. In addition to the 17p deletion, as assessed by the central laboratory, 83 (72.8%) of 114 subjects with available data were positive for TP53 gene mutations on the other allele, as assessed per local laboratory. Of the 144 subjects with available data, 22.9% harboured the 11q deletion, 81.3% harboured the 13q deletion and 19.4% were positive for 12q trisomy, as assessed by central laboratory (Table 20).

Table 20. Chromosomal Aberrations – All Treated Subjects

Characteristic Result	Main Cohort (N = 107) n (%)	Safety Expansion Cohort (N = 38) n (%)	Total (N = 145) n (%)
11q Deletion Status (Central Laboratory)			
Deleted	30 (28.0)	3 (8.1)	33 (22.9)
Not deleted	77 (72.0)	34 (91.9)	111 (77.1)
Missing	0	1	1
13q Deletion Status (Central Laboratory)			
Deleted	90 (84.1)	27 (73.0)	117 (81.3)
Not deleted	17 (15.9)	10 (27.0)	27 (18.8)
Missing	0	1	1
12q Trisomy Status (Central Laboratory			

Characteristic Result	Main Cohort (N = 107) n (%)	Safety Expansion Cohort (N = 38) n (%)	Total (N = 145) n (%)
Positive	19 (17.8)	9 (24.3)	28 (19.4)
Negative	88 (82.2)	28 (75.7)	116 (80.6)
Missing	0	1	1
TP53 Mutation Status (Local Laboratory)			
Positive	60 (72.3)	23 (74.2)	83 (72.8)
Negative	17 (20.5)	8 (25.8)	25 (21.9)
Indeterminate	6 (7.2)	0	6 (5.3)
Missing	24	7	31

Results for primary efficacy outcome

Response Rate

The primary efficacy endpoint was ORR as assessed by the IRC in the first 70 subjects in the main cohort is summarized in Table 21.

Table 21. Overall Response as Assessed by the IRC – First 70 Subjects in the Main Cohort

Subject Response[a]	First 70 Subjects in the Main Cohort % (n)
Overall response rate (CR + CRi + nPR + PR)	77.1 (54)
95% CI[b]	[65.6, 86.3]
P value[c]	< 0.001
Complete remission rate (CR + CRi)	7.1 (5)
Nodular partial remission (nPR)	2.9 (2)
Partial remission (PR)	67.1 (47)
Non responder[d]	22.9 (16)

CI = confident interval; CR = complete remission; CRi = complete remission with incomplete bone marrow response; nPR = nodular partial remission; PR = partial remission [a]Partial response needed to be confirmed not less than 49 days apart for overall response. [b]95% confident interval is from the exact binomial distribution. [c]P value is from exact binomial distribution comparing venetoclax ORR to 40% historical control rate. [d]Subjects with progressive disease, stable disease, or incomplete data were considered non responders by the IRC.

Overall response rate assessed by IRC in all 107 subjects enrolled in the main cohort and the ORR assessed by the Investigator in all 107 subjects is reported in Table 22.

Table 22. Overall Response – All Subjects in the Main Cohort

Subject Response[a]	IRC Assessment Main Cohort (N = 107) % (n)	Investigator Assessment Main Cohort (N = 107) % (n)
Overall response rate (CR + CRi +	79.4 (85)	73.8 (79)

Subject Response[a]	IRC Assessment Main Cohort (N = 107) % (n)	Investigator Assessment Main Cohort (N = 107) % (n)
nPR + PR)		
95% CI[b]	[70.5, 86.6]	[64.4, 81.9]
Complete remission rate (CR + CRi)	7.5 (8)	15.9 (17)
95% CI[b]	[3.3, 14.2]	[9.5, 24.2]
Nodular partial remission (nPR)	2.8 (3)	3.7 (4)
Partial remission (PR)	69.2 (74)	54.2 (58)
No response[c]	20.6 (22)	--[c]
Stable disease	--[c]	22.4 (24)
Disease progression	--[c]	1.9 (2)
Incomplete data	--[c]	1.9 (2)[d]

CI = confident interval; CR = complete remission; CRi = complete remission with incomplete bone marrow response; nPR = nodular partial remission; PR = partial remission. [a]Partial response needed to be confirmed not less than 49 days apart for overall response.[b]95% confident interval is from the exact binomial distribution. [c]The IRC assessed the overall response in the main cohort. Subjects with progressive disease, stable disease, or incomplete data were considered non responders by the IRC. [d]Subject [information redacted] discontinued venetoclax after 15 days of treatment. Subject [information redacted] withdrew consent after 1 day of treatment.

Overall, per IRC assessment, the majority of subjects (85/107 subjects; 79.4%) achieved a response. Complete remission (CR + CRi) was reported in 7.5% of subjects (8/107), including for 6 subjects achieving CR and 2 subjects achieving CRi.

Per investigator assessment, the ORR was 73.8% (79/107 subjects). Complete remission (CR + CRi) was reported in 15.9% of subjects (17/107), including for 14 subjects achieving CR and 3 subjects achieving CRi (Table 22).

Of note, 11 subjects experienced events that lead to dose interruption of > 28 days (range 29 to 141 days). Despite prolonged dose interruptions in these 11 subjects, ORR remained 79.4%, by IRC.

As of the data cut-off of this interim CSR, the PR rate (PR + nPR), per IRC assessment, for all treated subjects in the main cohort was 72.0% (95% CI: 62.5, 80.2), with 74 subjects achieving PR and 3 subjects achieving nPR (Table 22). Among the subjects achieving PR by IRC, 16 subjects showed absence of leukemic infiltrate in their bone marrow based on morphological and immunohistochemical analysis. Of note, 1 additional subject with absence of leukemic infiltrate at a morphological analysis of their bone marrow was categorized as a non-responder by the IRC. In total, 17 subjects (17.7%) of the 96 assessed as PR (excluding nPR) or non-responders by IRC had no evidence of CLL in the bone marrow based on standard immunohistochemical evaluation.

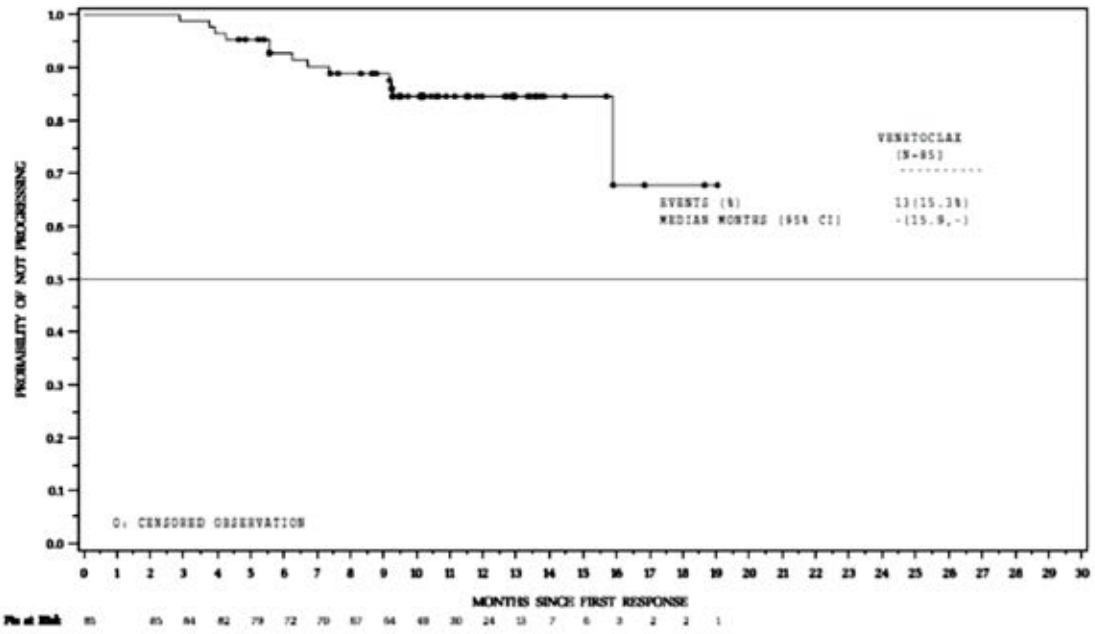
The PR rate (PR + nPR), per investigator assessment, for all treated subjects in the main cohort was 57.9% (95% CI: 48.0, 67.4), with 58 subjects achieving PR and 4 subjects achieving nPR.

Results for other efficacy outcomes

Duration of Overall Response

The median DOR had not been reached. As of the data cut-off of this interim CSR, per IRC assessment, DOR was evaluated in 85 subjects in the main cohort who had a record of first response (CR, CRi, PR, or nPR). The Kaplan-Meier estimate of the proportion of subjects with a durable response at 12 months was 84.7% (95% CI: 74.5%, 91.0%), per IRC assessment (Figure 13).

Figure 13. Kaplan-Meier Plot of Duration of Overall Response – IRC Assessment

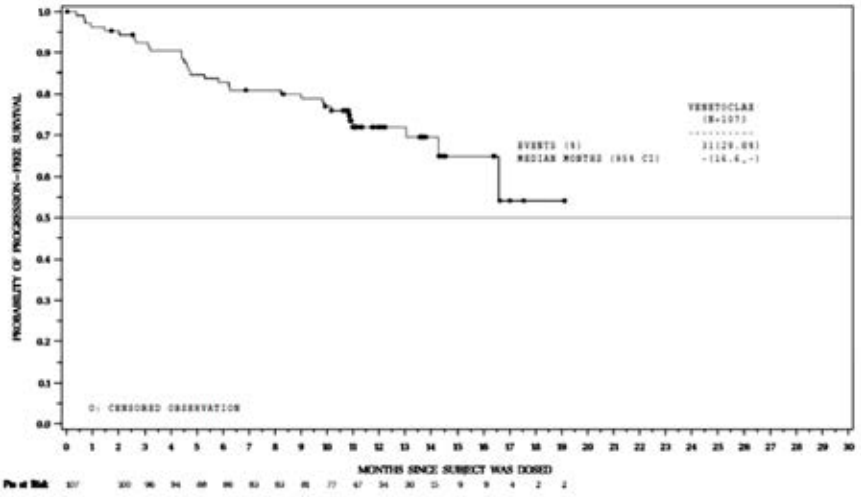


The Kaplan Meier estimate of the proportion of subjects achieving deep responses (CR, CRi, nPR) by IRC and with a durable response at 12 months was 100% (95% CI: 100%, 100%) compared to 82.6% (95% CI: 71.4%, 89.8%) in subjects achieving PR, by IRC.

Progression-Free Survival

The median duration of progression free-survival had not been reached. The Kaplan-Meier estimate of the proportion of subjects with PFS at 12 months was 72.0% (95% CI: 61.8%, 79.8%), based on IRC assessment (Figure 14).

Figure 14. Kaplan-Meier Plot of Progression-Free Survival IRC Assessment



Event-Free Survival

The median duration of event-free survival had not been reached. The Kaplan-Meier estimate of the proportion of subjects with event-free survival atv12 months was 70.0% (95% CI: 60.0%, 77.9%), per IRC assessment.

Time to tumour Progression

The median duration of time to tumour progression had not been reached. The Kaplan-Meier estimate of the proportion of subjects without progression at 12 months was 76.9% (95% CI: 67.0%, 84.2%), per IRC assessment. A total of 24 subjects experienced disease progression while on study.

Time to First Response

In order to consider a subject a responder, clinical response (PR or CR) was to be confirmed after at least 8 weeks by radiologic assessment. If the radiologic assessment confirmed a CR, then a bone marrow biopsy was to be performed as soon as possible to confirm the CR. For determination of CR, both the radiologic assessment and bone marrow were required to be negative.

Per IRC assessment, 6 (5.6%) subjects experienced CR, 2 (1.9%) subjects experienced CRi, 74 (69.2%) subjects experienced PR, and 3 (2.8%) subjects experienced nPR. For these 85 subjects, the median time to first response was 0.8 months (range: 0.1 to 8.1 months). Of the 8 subjects achieving CR/CRi, the median time to CR/CRi was 8.2 months (range: 3.0 to 16.3).

Overall Survival

A total of 17 (15.9%) subjects in the main cohort died. Therefore, 90 (84.1%) subjects in the main cohort were still alive as of the data cut-off date. The Kaplan-Meier estimate of the proportion of subjects surviving at 12 months was 86.7% (95% CI: 78.6%, 91.9%).

Subjects Who Received a Stem Cell Transplant

As of the data cut-off date for this interim report, 3 (2.8%) subjects in the main cohort subsequently received a stem cell transplant. These subjects achieved best responses of CR, PR, and PR by IRC assessment; and CR, CRi, and PR by investigator assessment, respectively. At the time of the data cut of the interim report, all 3 subjects remained disease free after approximately 2 months, 1 month and 11 months from the transplant, respectively.

Minimal Residual Disease Response Rate

MRD negativity, a very sensitive measure of defining no measurable remaining tumour load after treatment and, therefore, an indicator of the depth of response to treatment in CLL, was

assessed in this study. Low MRD levels during and after therapy are known to be associated with longer PFS and OS.

No detectable MRD was reported in the peripheral blood of 18 subjects (sensitivity < 10^{-4}). Ten of the 18 subjects had also an MRD assessment in the bone marrow; 6 subjects did not show any evidence of minimal residual disease in the bone marrow. Detectable MRD was reported in 27 subjects: 18 subjects (16 in the peripheral blood and 2 in the bone marrow) with intermediate level of MRD (10^{-4} and 10^{-2}); 8 subjects with high level of MRD (10^{-2}); and 1 subject with an atypical phenotype and therefore had no percentage of CLL cells provided.

Time to Next Anti-CLL Treatment

The TTNT was defined as the number of days from the date of the first dose of venetoclax to the date of first dose of a new anti-CLL treatment or death from any cause. A total of 25 (23.4%) subjects in the main cohort were identified as receiving a new anti-CLL treatment. Kaplan-Meier estimate of the proportion of subjects not receiving a new anti-CLL treatment or experiencing death at 12 months was 79.1% (95% CI: 70.0%, 85.7%).

7.1.2. Other clinical efficacy studies

7.1.2.1. Study M12-175

Study M12-175, a key supportive study, was a dose escalation and safety expansion Phase I study evaluating the safety and pharmacokinetics of venetoclax in subjects with R/R CLL/SLL.

Study design, objectives, locations and dates

The primary objectives of this study were to:

- Assess the safety profile, characterise pharmacokinetics, determine the maximum tolerated dose (MTD), determine the recommended Phase II dose (RPTD), including the lead-in (that is, ramp-up) period regimen of venetoclax in subjects with relapsed or refractory CLL and NHL.
- Assess food effect in cohorts 1 to 6 of the NHL dose-escalation portion of the study.

The secondary objectives were to:

- Evaluate preliminary efficacy data regarding the effect of venetoclax on progression-free survival (PFS), overall response rate (ORR), time to tumour progression (TTP), overall survival (OS), and duration of response.
- Evaluate biomarkers and pharmacogenetics.
- Assess minimal residual disease (MRD), assessed in the peripheral blood and/or bone marrow either by flow cytometry or real time polymerase chain reaction (PCR) in subjects with CLL.
- Note: study objectives were revised during the study
- To allow subjects with SLL to enter the study.
- To include subjects with NHL (Arm B) in the study, and add a primary objective to assess food effect in NHL cohorts 1 to 6 of the dose-escalation portion, but not the subsequent NHL cohorts as sufficient data had been collected.
- To add a primary study objective of determining the RPTD in subjects with CLL and NHL.
- To add a primary study objective of determining the ramp-up period regimen for subjects with CLL and NHL.
- To add evaluation of MRD in subjects with CLL who achieve CR/complete remission with incomplete marrow recovery (CRi).

Inclusion and exclusion criteria

Subjects with relapsed or refractory CLL/SLL participated in Arm A of this study. Subjects with CLL/SLL had to be relapsed following, or be refractory to standard treatments such as fludarabine-based regimens (fludarabine [F], fludarabine plus cyclophosphamide [FC], FR [fludarabine plus rituximab], FCR [fludarabine plus cyclophosphamide and rituximab]) or alkylator (chlorambucil, bendamustine)-based regimens.

Subjects with relapsed or refractory NHL participated in Arm B of this study. Subjects with NHL had to be relapsed following or be refractory to standard treatments such as R-CHOP, R-CVP or fludarabine based regimens. In addition, the subjects were unable to tolerate other available therapies or no other therapies were available. Preclinical findings supported the possibility of efficacy in this patient population.

Inclusion

Subjects underwent screening procedures within 21 days prior to the first study drug administration, as well as tumour assessment, including computed tomography (CT) scan (or magnetic resonance imaging [MRI], positron emission tomography [PET], PET-CT). Bone marrow aspirate and biopsy could be performed within 21 days of screening visit unless a bone marrow biopsy and/or aspirate and biopsy was obtained within the previous 12 weeks of starting study drug without intervening treatment and was representative of the subject's existing disease. Adult male and female subjects who met the inclusion criteria and did not meet any of the exclusion criteria were eligible for enrolment into the study

A subject was eligible for study participation if he/she met the following criteria.

- Subject had to be ≥ 18 years of age.
- Subject must have had either:
    a. Arm A – relapsed or refractory CLL/SLL
        i. Subject required treatment in the opinion of the investigator.
        ii. Subject had relapsed following or was refractory to standard treatments such as fludarabine-based regimens (F, FC, FR, FCR) or alkylator (chlorambucil, bendamustine) based regimens.
        iii. In addition, there were no other curative options, and the subject had exhausted options that would be considered standard of care.

or

    b. Arm B – relapsed or refractory NHL
        i. Subject had histologically documented diagnosis of NHL as defined in the World Health Organization (WHO) classification scheme, except as noted in Exclusion Criteria.
        ii. Subject required treatment in the opinion of the investigator.
        iii. Subject had relapsed following or were refractory to standard treatments such as R-CHOP, RCVP, or fludarabine-based regimens.
        iv. In addition, there were no other curative options, and the subject had exhausted options that would be considered standard of care.
        v. Subjects with other lymphoproliferative diseases may have been considered in consultation with the AbbVie.
- Subject had an ECOG performance score of ≤ 1.

- Subject had adequate bone marrow independent of growth factor support, per local laboratory reference range at screening as follows:
    a. Absolute neutrophil count (ANC) ≥ 1000/μL;
        i. An exception was allowed for subjects with an ANC < 1000/μL and bone marrow heavily infiltrated with underlying disease (approximately 80% or more); these subjects were allowed to use growth factor to achieve the ANC eligibility criteria per discussion with the AbbVie medical monitor;
    b. Platelets ≥ 30,000/mm3, beginning with Amendment 9 (≥ 50,000/mm3 under Amendments 1 – 8) (entry platelet count had to be independent of transfusion within 14 days of first dose);
        i. Haemoglobin ≥ 8.0 g/dL.
- Subject had adequate coagulation, renal, and hepatic function, per laboratory reference range at screening as follows:
    a. Activated partial thromboplastin time (aPTT) and prothrombin time (PT) not to exceed 1.2 × upper limit of normal (ULN);
    b. Calculated creatinine clearance ≥ 50 mL/min using 24-h Creatinine Clearance OR modified Cockcroft-Gault equation (using Ideal Body Mass [IBM] instead of Mass):

        eCCr = (140 – Age) × IBM (kg) × [0.85 if Female]/72 × Serum Creatinine (mg/dL)

        Or, if serum creatinine is in μmol/L:

        eCCr = (140 – Age) × IBM (kg) × [1.23 if Male, 1.04 if Female]/Serum Creatinine (μmol/L)

        Ideal Body Mass was to be used:

        IBM (kg) = [(height cm – 154) × 0.9] + (50 if Male, 45.5 if Female)

        eCCr = estimated creatinine clearance
    c. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 × the ULN of institution's normal range; bilirubin ≤ 1.5 × ULN. Subjects with Gilbert's Syndrome could have bilirubin > 1.5 × ULN, per discussion between the investigator and AbbVie medical monitor.
- Females of childbearing potential and non-sterile males were to practice at least one of the following methods of birth control with partner(s) throughout the study and for 90 days after discontinuing study drug:
    a. Total abstinence from sexual intercourse as the preferred lifestyle of the subject; periodic abstinence was not acceptable;
    b. Surgically sterile partner(s); acceptable sterility surgeries were: vasectomy, bilateral tubal ligation, bilateral oophorectomy, or hysterectomy;
    c. Intrauterine device;
    d. Double-barrier method (contraceptive sponge, diaphragm, or cervical cap with spermicidal jellies or cream AND a condom);
    e. Hormonal contraceptives (oral, parenteral, vaginal ring, or transdermal) for at least 3 months prior to study drug administration. If hormonal contraceptives were to be used, the specific contraceptive must have been used for at least 3 months prior to study drug administration.

- Females of childbearing potential (that is, not postmenopausal for at least 2 years or surgically sterile) had to have negative results for pregnancy test performed:
    a. At screening on a serum sample obtained within 14 days prior to the first study drug administration, and
    b. Prior to dosing on a urine sample obtained on the first day of study drug administration, if it had been > 7 days since obtaining the serum pregnancy test results.
- Subject had to voluntarily sign and date an informed consent, approved by an IEC/IRB, prior to the initiation of any screening or study-specific procedures.
- NHL subjects who had a history of an autologous stem cell transplant (for example, bone marrow) had to be > 6 months' post-transplant (prior to the first dose of study drug) and have adequate bone marrow independent of any growth factor support (with the exception of subjects with bone marrow that was heavily infiltrated with underlying disease [80% or more] who were allowed to use growth factor support to achieve ANC eligibility criteria), per laboratory reference range at screening as follows:
    a. ANC ≥ 1,500/µL;
    b. Platelets ≥ 75,000/mm3 (entry platelet count had to be independent of transfusion within 14 days of screening);
    c. Haemoglobin ≥ 10.0 g/dL.
- Subjects with high risk CLL/SLL and MCL subjects (high risk of TLS) required preapproval by the AbbVie medical monitor prior to enrolment.
- Male subjects were to refrain from sperm donation starting from first study drug administration until 90 days after the last dose of study drug.

Exclusion

A subject was not eligible to participate in this study, if any of the following criteria applied:

- CLL subject had undergone an allogeneic or autologous stem cell transplant.
- Subject had known positivity for human immunodeficiency virus (HIV) (due to potential drug-drug interactions between anti-retroviral medications and venetoclax, as well as anticipated venetoclax mechanism-based lymphopenia that may have potentially increased the risk of opportunistic infections and potential drug-drug interactions with certain anti-infective agents).
- Subject required the use of warfarin (due to potential drug-drug interactions that may have potentially increased the exposure of warfarin and complications of this effect).
- Subject had received a monoclonal antibody for anti-neoplastic intent within 8 weeks prior to the first dose of study drug.
- Subject had received any of the following within 14 days prior to the first dose of study drug, or had not recovered to less than grade 2 clinically significant adverse effect(s)/toxicity(s) of the previous therapy:
    a. Any anti-cancer therapy including chemotherapy or radiotherapy;
    b. Investigational therapy, including targeted small molecule agents.
- Subject had received the following within 7 days prior to the first dose of study drug:
    a. Steroid therapy for anti-neoplastic intent;

b. Cytochrome P450 3A (CYP3A) inhibitors such as fluconazole, ketoconazole, and clarithromycin;

c. Potent CYP3A inducers such as rifampin, carbamazepine, phenytoin, and St. John's Wort;

d. Weak/moderate CYP3A inducers such as rufinamide, pioglitazone and modafinil (only for subjects who participated in cohorts 1 – 6 in the Arm B [NHL] dose-escalation portion of the study).

- Subject had consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit within 3 days prior to the first dose of study drug.
- Subject had a history of a prior significant toxicity other than thrombocytopenia from another Bcl-2 family protein inhibitor.
- Subject had a cardiovascular disability status of New York Heart Association Class ≥ 2. Class 2 is defined as cardiac disease in which patients are comfortable at rest but ordinary physical activity, results in fatigue, palpitations, dyspnea, or anginal pain.
- Subject had a significant history of renal, neurologic, psychiatric, pulmonary, endocrinologic, metabolic, immunologic, cardiovascular, or hepatic disease that in the opinion of the investigator would adversely affect his/her participation in this study. For subjects who required an intervention for any above diseases within the past 6 months, a discussion with the investigator and the AbbVie medical monitor had to occur.
- A female subject was pregnant or breast-feeding.
- Subject had a history of other active malignancies other than CLL or NHL within the past 3 years prior to study entry, with the exception of:

  a. Adequately treated in situ carcinoma of the cervix uteri;

  b. Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin;

  c. Previous malignancy confined and surgically resected (or treated with other modalities) with curative intent.

- Subject had malabsorption syndrome or other condition which precluded enteral route of administration.
- Subject exhibited evidence of other clinically significant uncontrolled condition(s) including, but not limited to:

  a. Uncontrolled systemic infection (viral, bacterial, or fungal);

  b. Diagnosis of fever and neutropenia within 1 week prior to study drug administration.

- NHL subject had undergone an allogeneic stem cell transplant.
- NHL subject had been diagnosed with Post-Transplant Lymphoproliferative Disease (PTLD), Burkitt's lymphoma, Burkitt-like lymphoma, or lymphoblastic lymphoma/leukaemia.
- Subject had active and uncontrolled autoimmune cytopenias (for 2 or more weeks), including autoimmune hemolytic anaemia (AIHA) and idiopathic thrombocytopenic purpura (ITP).

Study treatments

Throughout the course of the study, substantial revisions were made to the dosing plan and study conduct of both the dose-escalation cohorts and the expanded safety cohorts of Arm A (CLL/SLL) and Arm B (NHL) in response to the observed risk of tumour lysis syndrome (TLS).

There were 4 major amendments related to TLS management (Amendments 3, 5, 8, and 9). Changes to venetoclax dosing for CLL/SLL as a result of protocol changes are summarized in Table 23, and changes to venetoclax dosing for NHL are shown in Table 24.

Table 23. Summary of Major Changes to Study Conduct – CLL/SLL

	Pre-May 2013		Post-May 2013	
	Amendment 3	Amendment 5	Amendment 8	Amendment 9
Cohorts Initiated	Amendments 3 and 4: DE cohorts 2 to 6[a]	Amendments 5 to 7: DE cohorts 7 and 8[a]	SE cohort[a]	SE cohort[a]
Observed TLS events and notes on analysis	Prior to Amendment 3: DLTs of LTLS in all 3 CLL subjects in cohort 1 at first doses of 100 mg or 200 mg.	Prior to Amendment 5: CLL/SLL: 1 SAE of TLS with acute renal failure requiring dialysis at first 50 mg dose (cohort 4).	Prior to Amendment 8: 2 deaths in setting of TLS (Dec 2012) Study M12-175 (cohort 8, second 1200 mg dose–sudden death) Study M13-365 (first 50 mg dose – hyperkalemiain setting of TLS) Partial clinical hold to venetoclax program – Subjects dosing at 800 mg and 1200 mg were dose reduced to ≤ 600 mg. First TLS analysis (11 Jan 2013) across all venetoclax studies since study start: 77 patients with CLL/SLL analyzed. A total of 12 AEs of TLS observed.	During Amendment 9: Second TLS analysis (17 Jan 2014) in 58 new subjects with CLL/SLL completing ramp-up period under revised TLS guidelines (Amendments 8 and 9): No new serious or nonserious AEs of CTLS or LTLS
New Dose and Regimen	DE cohorts: Amendment 3 introduced 2- to 3-week ramp-up period with a lower starting dose (cohorts 2 through 8). New starting dose: ≤ 50 mg Step-up doses: 100 to 150 mg Target cohort doses: 150 to 1200 mg Highest DCD administered = 1200 mg (beginning with cohort 8)		SE cohort: 5-week ramp-up period, further lowered starting dose. Starting dose: 20 mg (W1D1) →V50 mg (W1D2 to W1D7) →100 mg (W2) → 200 mg (W3) →VDCD (starting W4) Highest DCD = 400 mg	SE cohort: 5-step ramp-up period with longer start dose. Starting dose: 20 mg (W1) → 50 mg (W2) →100 mg (W3) → 200 mg (W4) → DCD (starting W5)

Pre-May 2013			Post-May 2013	
				Highest DCD = 400 mg
	Pre-May 2013		**Post-May 2013**	
	Amendment 3	Amendment 5	Amendment 8	Amendment 9
Cohorts Initiated	**Amendments 3 and 4: DE cohorts 2 to 6[a]**	**Amendments 5 to 7: DE cohorts 7 and 8[a]**	**SE cohort[a]**	**SE cohort[a]**
CLL/SLL: Major changes to manage risk of TLS	Starting with cohort 2: Hydration + uric acid reducing agent all subjects Hospitalization based on risk assessment Staggered enrolment in CLL/SLL and NHL cohorts (second subject in new cohort not dosed until at least 1 week after first subject's Week 1 Day –7 dose)	Starting with cohort 7: Mandatory Day 1 hospitalization after first dose (CLL/SLL only) Mandatory prophylaxis for CLL/SLL and NHL: o Hydration (Oral: 1 – 2 L) 24 h prior to treatment; oral/IV hydration (at least 1 L) on day of treatment) o Uric acid reducing agent 12 to 24 h prior to treatment o Rasburicase strongly recommended for high-risk TLS. o More frequent lab chemistry and hematology assessments High disease burden and risk: Bulky disease (> 10 cm lymph node) WBC > 25,000 Preexisting renal impairment	Starting with SE cohort: Assessment of risk (low, medium, high) based on node size + ALC (High-risk: node size ≥ 5 cm AND ALC ≥ 25 × 10^9/L or any node size ≥ 10 cm) Mandatory hospitalization regardless of tumour burden at 20 mg and 50 mg (all) and dose-escalation (high-risk) Enhanced TLS prophylaxis/monitoring: o Uric acid reducer 72 h before first dose o Mandatory rasburicase predose as prophylaxis (high-risk) o Hydration (mandatory IV for first 20 and 50 mg doses; oral or IV hydration for subsequent escalations depending on risk) Further increased frequency of lab chemistry assessments More detailed summary of TLS prophylaxis and	More details in protocol and rest of Section 9.0 of CSR (particularly Section 9.5.1.9.2, Prophylaxis and Management of TLS)

Pre-May 2013			Post-May 2013	
			management in	

AE = adverse event; ALC = absolute lymphocyte count; CLL = chronic lymphocytic leukaemia; CTLS = clinical tumour lysis syndrome; DCD = designated cohort dose; DE = dose escalation, IV = intravenous; LTLS = laboratory tumour lysis syndrome; MCL = mantle cell lymphoma; SAE = serious adverse event; SE = safety expansion; SLL = small lymphocytic lymphoma; TLS = tumour lysis syndrome; W1D1= Week 1 Day 1, etc.; WBC = white blood cells a. DCDs were: cohort 2 = 150 mg; cohort 3 = 200 mg; cohort 4 = 300 mg; cohort 5 = 400 mg; cohort 6 = 600 mg; cohort 7 = 800 mg; cohort 8 = 1200 mg; and, safety expansion cohort = 400 mg. Note: The protocol amendments that had major revisions to management of TLS were Amendments 3, 5, and 8.

Table 24. Changes to venetoclax dosing for NHL changes to venetoclax dosing for NHL

Pre-May 2013			Post-May 2013	
	Amendment 3	Amendment 5	Amendment 8	Amendment 9
Cohorts Initiated	Amendments 3 and 4: DE cohorts 1 to 5[a]	Amendments 5 to 7: DE cohorts 6[a]	DE cohorts 7A (MCL), 7B (all other NHL), 8A (MCL), 8B (other NHL), 8C (RS); and SE cohort[a]	DE cohorts 8A (MCL) and 9A (MCL); and SE cohort[a]
Observed TLS events and notes on analysis	Prior to Amendment 3: None	Prior to Amendment 5: NHL: 1 nonserious LTLS AE	Prior to Amendment 8: MCL: 1 nonserious LTLS AE Partial clinical hold to venetoclax program –	During Amendment 9: None Second TLS analysis
New Dose and Regimen	DE cohorts: 2 to 3-week ramp-up period for doses (cohorts 1 through 6, all NHL): Starting dose: 50 to 400 mg Step-up doses: 100 to 400 mg (none for cohorts 5 and 6) DCD: 200 to 900 mg MCL subjects starting dose 200 mg (starting in cohort 6).		DE cohorts: ramp-up period in Amendment 8 NHL: Starting dose 300 mg, escalate 300 → 600 → 900 mg weekly. Highest DCD during DE = 1200 mg MCL cohort 7A: Starting dose 20 mg W1D1, escalate → 50 mg (W1D2 to W1D7) → 100 mg (W3) → 200 mg (W4) → DCD (W5). Highest DCD = 400 mg MCL cohort 8A: Starting dose 20 mg W1D1, escalate → 50 mg (W1D2 to W1D7) → 100 mg (W3) → 200 mg (W4) → 400 mg (W5) → DCD (W6).	DE MCL cohort 9A: Starting dose: 100 mg (W1) → 200 mg (W2) → 400 mg (W3) → 800 mg (W4) → 1200 mg (W5) Highest DCD for MCL = 1200 mg SE cohort: (FL and DLBCL) Actual ramp-up for both FL and DLBCL as follows: 400 mg (W1) → 800 mg (W2) → 1200 mg (W3)

Pre-May 2013			Post-May 2013	
			Highest DCD = 800 mg DLBCL with RS: first at 20 mg, escalate weekly: → 50 mg → 100 mg → 200 mg →DCD Highest DCD for RS = 400 mg	
Major changes to manage risk of TLS	Amendment 3: Starting with cohort 2: Amendment 5: Starting with cohort 7: Hydration + uric acid reducing agent all subjects Hospitalization based on risk assessment	Starting with cohort 7A: MCL: TLS prophylaxis/management plan similar to that of CLL/SLL. Assessment of risk (low, medium, and high) based on node size (high-risk: any node ≥ 10 cm). All other NHL: Risk assessment (high risk or not) based on node size (< 10 vs. ≥ 10 cm) Oral uric acid reducer at least 72 hrs prior to first dose Prophylactic rasburicase if needed Mandatory hospitalization for high risk subjects for first dose IV hydration (hospitalized subjects) or oral (outpatient) Increased frequency of lab chemistry assessments	Starting with SE cohort: Assessment of risk (low, medium, high) based on node size + ALC (High-risk: node size ≥ 5 cm AND ALC ≥ 25 × 10^9/L or any node size ≥ 10 cm) Mandatory hospitalization regardless of tumour burden at 20 mg and 50 mg (all) and dose-escalation (high-risk) Enhanced TLS prophylaxis/monitoring: o Uric acid reducer 72 h before first dose o Mandatory rasburicase predose as prophylaxis (high-risk) o Hydration (mandatory IV for first 20 and 50 mg doses; oral or IV hydration for subsequent escalations depending on risk) Further increased frequency of lab chemistry assessments More detailed summary of TLS prophylaxis and management in	Minor changes. MCL: first dose → 3+ ramp-up step doses → DCD NHL: first dose → ramp-up dose → DCD

ALC = absolute lymphocyte count, CLL = chronic lymphocytic leukaemia; DCD = designated cohort dose; DE = dose-escalation, DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; IV = intravenous; LTLS =

laboratory tumour lysis syndrome; MCL = mantle cell lymphoma; NHL = non-Hodgkin lymphoma; RS = Richter's Syndrome; SAE = serious adverse event; SE = safety expansion; SLL = small lymphocytic lymphoma; TLS = tumour lysis syndrome; W1D1= Week 1 Day 1, etc.; WBC = white blood cells; WM = Waldenstrom's macroglobulinemia. [a]DCDs were: cohort 1 = 200 mg; cohort 2 = 300 mg; cohorts 3, 7A (MCL), and 8C (DLBCL with RS) = 400 mg; cohorts 4 and 5 = 600 mg; cohort 8A (MCL) = 800 mg; cohorts 6 and 7B (all other NHL) = 900 mg; cohorts 8B (other NHL), 9A (MCL), and safety expansion (FL and DLBCL) = 1200 mg.

Note: The protocol amendments that had major revisions to management of TLS were Amendments 3, 5, and 8. Source: Protocol Amendment 3 was finalised on 19 July 2011 after the initial 3 CLL subjects in this study experienced laboratory TLS following the first venetoclax dose of 100 or 200 mg. Amendment 3 reduced the initial dose of venetoclax for CLL/SLL to 50 mg, established a 2- to 3-week ramp-up period with weekly dose escalation to the designated cohort dose, set the maximum daily dose at 1200 mg, and implemented hydration and uric acid control for all subjects. Amendment 5 enacted mandatory Day 1 hospitalisation of CLL/SLL subjects, more stringent TLS prophylaxis measures (hydration, uric acid control, and laboratory assessments), but no further dosing changes.

In December 2012, 2 fatal events occurred in the setting of TLS in CLL subjects who had failed multiple prior therapies and had a high tumour burden (that is, lymphadenopathy ≥ 10 cm, high absolute lymphocyte count [ALC]). The first death occurred within 24 h after administration of the subject's first dose of 50 mg. The second death occurred within 48 h after the subject had dose-escalated to 1200 mg. This resulted in a sponsor-initiated partial clinical hold for the venetoclax program (no enrolment of new subjects and immediate reduction in venetoclax dosing to ≤ 600 mg for existing subjects), comprehensive review of all safety data available from venetoclax studies, and modifications to the dosing regimen. Protocol Amendments 1 to 7 were called pre-May 2013; 56 CLL/SLL and 32 NHL subjects were dosed under these amendments

In May 2013, the venetoclax clinical program was restarted under Amendment 8 with more gradual ramp-up over 5 weeks, starting at 20 mg with final dose of 400 mg in CLL/SLL subjects, enhanced monitoring, and TLS prophylaxis measures, and additional guidance for investigators. NHL subjects also had modifications including ramp-up dosing and enhanced TLS monitoring and prophylaxis. Subsequently, Amendment 9 implemented a 20 mg initial dose for CLL/SLL subjects for 1 full week. Protocol Amendments 8 to 10 were called post-May 2013; 60 CLL/SLL and 74 NHL subjects were dosed under these amendments.

Dose-Escalation Cohorts

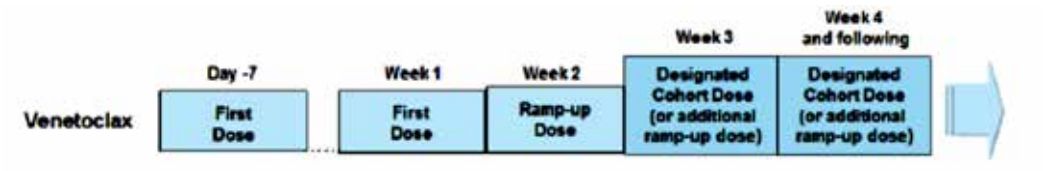
During the first week of the dose-escalation portion for Arm A (CLL/SLL) or Arm B (NHL cohorts 1 to 6 only), venetoclax was administered for a single day on Week 1 Day –7 (Week 1 Day –3 in Arm A cohort 1).

For Arm B (NHL) dose-escalation cohorts starting with cohort 7, the first dose was administered on Week 1 Day 1, with no first/single dose, because the investigation of food effect had been concluded.

Dosing Scheme for Subjects with CLL/SLL

A sample dosing schedule for Week 1 and all subsequent weeks for the CLL/SLL arm is depicted in Figure 15.

Figure 15. Sample Dosing Schematic for Ramp-Up to Designated Cohort Dose – Dose-Escalation Cohorts – Arm A (CLL/SLL)



The actual doses administered during dose-escalation in Study M12-175 Arm A are shown in Table 25. Additional modifications due to TLS were made starting with Amendment 8, post-May 2013; however, these modifications affected only the safety expansion cohort.

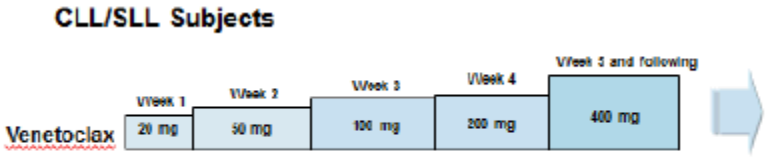
Table 25. Venetoclax Dose Escalation in Study M12-175, Arm A (Subjects with CLL/SLL)

Venetoclax				
Cohort	Subjects Enrolled (N)	First Dose (mg)	First Dose Increase (mg)	Designated Cohort Dose (mg)
2	6	50[a]	100	150
3	6	50[a]	100	200
4	7	50	100	300
5	7	50[a]	100	400
6	15	50	150[b]	600
7	7	50	150	800[c]
8	5	50	150	1200[c]

a) Three subjects (1 each in cohorts 2, 3, and 5) received venetoclax 20 mg as the first dose due to very bulky disease and lymphocytosis. b)In cohort 6, an extra week with a second dose increase of 400 mg was added prior to the designated cohort dose of 600 mg. c)Subjects at the 800 and 1200 mg dose were lowered to 600 mg following the 2 deaths in the setting of TLS in subjects with CLL/SLL and the subsequent partial clinical hold on December 2012. Note: Cohort 1 subjects were dosed at 100 mg and 200 mg venetoclax; there were no ramp-up doses.

Once the MTD was declared, a cohort of approximately 60 additional CLL/SLL subjects in Arm A and a cohort of approximately 20 additional DLBCL de novo subjects and approximately 20 additional follicular lymphoma subjects in Arm B were to be enrolled in expanded safety portions of the study at the RPTD and schedule. The dosing schedule for the expanded safety portions of the CLL/SLL subjects is depicted in Figure 16.

Figure 16. Dosing Schematic for Ramp-Up to Designated Cohort Dose – Safety Expansion Cohorts – Arm A (CLL/SLL)



Patients continued to receive daily venetoclax until disease progression or unacceptable toxicity. Supportive care, anti-infection prophylaxis, and growth-factor support for substantial neutropenia were provided according to institutional standards of care.

Efficacy variables and outcomes

All efficacy analyses were exploratory in nature. The exploratory efficacy endpoints included ORR, PFS, TTP, OS, duration of overall response, MRD, and ECOG performance status.

Sample size

This was a dose-escalation study. The number of subjects required depended upon the toxicities observed as the trial progressed, but it was expected that the dose-escalation portion of both Arm A (CLL/SLL) and Arm B (NHL) would include approximately 56 and 55 subjects, respectively. The expected number of subjects in the Arm B dose-escalation portion of the study

(approximately 55) should be adequate for a preliminary assessment of the effects of food on the pharmacokinetics of venetoclax. Once the MTD was reached for each arm, approximately 60 additional CLL/SLL subjects in Arm A and approximately 20 additional DLBCL de novo subjects and 20 additional follicular lymphoma subjects in Arm B were enrolled into expanded safety portions of this study at the MTD of venetoclax determined for that arm.

Statistical methods

Unless otherwise noted, for all statistical analyses, statistical significance was determined by a two-sided P value ≤ 0.05 (one-sided ≤ 0.025 where applicable).

Both efficacy and safety analyses were performed for all subjects in Arm A (CLL/SLL); only safety analyses were performed for subjects in Arm B (NHL). The 2 efficacy and safety analysis sets are presented in Table 26. Each set contains all subjects meeting the specified criteria who received at least 1 dose of venetoclax in either the dose escalation portion or the safety expansion portion of the study. Analyses using the All Treated Subjects analysis set were performed by arm (CLL/SLL or NHL).

Table 26. Data Analysis Sets for CLL/SLL and NHL Cohorts

Analysis Set	Subjects	Description	Analyses Performed
All Treated Subjects	CLL/SLL (Arm A); n = 116	All CLL/SLL subjects who received ≥ 1 dose of venetoclax	Efficacy and Safety: All Safety summaries were performed by dose cohort, dose categories (< 400 mg, = 400 mg, > 400 mg), and overall. All Efficacy analyses were performed for overall response rates (ORR, CR rate, nPR, PR rate) and by dose cohort and dose categories (< 400 mg, = 400 mg, > 400 mg).
	NHL (Arm B) N = 106	All NHL subjects who received ≥ dose of venetoclax	Safety: All Safety summaries were performed by dose cohort and overall.
All Treated CLL/SLL Subjects with 17p Deletion	CLL/SLL (Arm A) n = 24	All CLL/SLL (Arm A) subjects with 17p deletion who received ≥ 1 dose of venetoclax	Efficacy and Safety: All safety analyses were performed by dose cohort, dose categories (< 400 mg, = 400 mg, > 400 mg), and overall. All efficacy analyses were performed for overall response rates (ORR, CR rate, PR rate) and by dose cohort and dose categories (< 400 mg, = 400 mg, > 400 mg).

The following exploratory efficacy analyses were performed for Arm A in this interim CSR:

Progression-Free Survival

The distribution of PFS was estimated using Kaplan-Meier methodology. Median PFS and the corresponding 95% confidence interval (CI) were estimated. For a given subject, PFS was defined as the number of days from the date the subject started study drug to the date the subject experienced an event of disease progression (radiographic or clinical), or to the date of death if disease progression was not reached. All events of disease progression were included, regardless of whether the event occurred while the subject was still taking study drug or had previously discontinued study drug. Events of death were included for subjects who had not experienced disease progression, provided death occurred within 24 weeks of the date of the last available tumour evaluation. If a subject had not experienced an event of disease progression or death, then the subject's data was censored at the date of the last available evaluation for disease progression. The date of the last available evaluation was the date of the last visit at which a tumour assessment was performed. If a subject did not have any post baseline tumour assessment or clinical assessment for progression, the data were censored at the date of enrolment plus 1 day.

Overall Response Rate

The proportion of subjects with a response of CR, CRi, or nPR (only applicable for CLL/SLL subjects), or confirmed PR (a subsequent CT at approximately 8 weeks) based on a modified 2008 IWCLL updating of the NCI-WG 1996 guidelines for subjects with CLL were estimated and the corresponding 95% CI for the proportion were constructed. The exact binomial distribution was used to construct this CI.

Time to tumour Progression

Time to tumour progression for a given subject was defined as the number of days from the date the subject started study drug to the date of the subject's tumour progression. Time to tumour progression could be collected up to 12 weeks following the last available tumour evaluation. All events of tumour progression were included, regardless of whether the event occurred while the subject was still taking study drug, or after the subject discontinued study drug. If a subject had not progressed, then the data were censored at the last study visit at which a tumour assessment was performed. If a subject did not have any post baseline tumour assessment or clinical assessment for progression, the data were censored at the date of enrolment plus 1 day. The distribution of the time to tumour progression was estimated using Kaplan-Meier methodology. Median time to tumour progression and the corresponding 95% CI were estimated.

Overall Survival

Time to death for a given subject was defined as the number of days from the date the subject started study drug to the date of the subject's death. All events of death were included, regardless of whether the event occurred while the subject was still taking study drug, or after the subject discontinued study drug. If a subject had not died, then the data were censored at the date of the last study visit, the last contact date, or the date the subject was last known to be alive, whichever was last. The date of the last study visit was determined by selecting the last available date of the following study procedures for a subject: tumour assessment, clinical disease progression, physical examination, vital signs assessment, clinical laboratory collection, and performance status. The distribution of the time to death was estimated using Kaplan-Meier methodology. Median survival time and the corresponding 95% CI were estimated.

Duration of Response

The duration of overall response for a given subject was defined as the number of days from the day the criteria were met for CR, CRi, nPR or PR (whichever is recorded first) to the date that progressive disease was objectively documented or death. The reference for progressive disease was the smallest measurements recorded since the treatment started. If a subject was still responding, then the subject's data was censored at the last study visit at which a tumour

assessment was performed. Only subjects with an objective response were included in the analysis of duration of response. The analysis was not to be performed if ORR was less than 20%. The distribution of the duration of overall response was estimated using Kaplan-Meier Methodology.

Minimal Residual Disease (MRD)

MRD for enumeration of CLL cells (expressing for example, CD5, CD19, CD23, and CD79a) was assessed in bone marrow aspirate and/or peripheral blood using flow cytometry per local and/or designated lab. Peripheral blood and/or bone marrow aspirate was to be collected for all CLL subjects at least 8 weeks after the CR/CRi criteria for tumour response were first met. After CR/CRi status had been confirmed, MRD assessments were to be performed every 12 weeks until MRD negativity had been achieved (in peripheral blood). Once MRD negativity was achieved in the peripheral blood, MRD assessment was to be performed in the bone marrow. A subject was considered MRD-negative if there was < 0.01% CLL cells (< 1 CLL cell per 10,000 leukocytes) and sensitivity of the assay used was ≤ 0.01 or 10^{-4}.

ECOG Performance Status

For the ECOG performance scale, descriptive statistics were summarised for each assessment. In addition, a mean change from baseline to each assessment was summarised.

Enrolment of Subjects

A total of 277 subjects were screened, of whom 55 were screen failures. As of the data cut-off date (10 February 2015), 222 subjects were enrolled and treated at 7 sites in the US (150 subjects) and 2 sites in Australia (72 subjects).

A total of 116 CLL/SLL subjects were enrolled in Arm A: 3 subjects in cohort 1 (200 mg), 6 subjects in cohort 2 (150 mg), 6 subjects in cohort 3 (200 mg), 7 subjects in cohort 4 (300 mg), 7 subjects in cohort 5 (400 mg), 15 subjects in cohort 6 (600 mg), 7 subjects in cohort 7 (800 mg), 5 subjects in cohort 8 (1200 mg), and 60 subjects in the safety expansion cohort (400 mg). Seven CLL/SLL subjects did not reach their designated cohort dose and 19 subjects escalated to above their designated cohort dose. The dose of venetoclax was reduced for 15 (12.9%) CLL/SLL subjects to manage adverse events. In addition, there were a limited number of subjects who dose reduced following a TLS event that occurred at the 1200 mg dose.

A total of 56 (48.3%) CLL/SLL subjects were still active in the study as of 10 February 2015, the date of data cut-off and 60 (51.7%) CLL/SLL subjects discontinued. The primary reasons for discontinuation were: disease progression (36 subjects, 31.0%; including Richter's syndrome for 15 of the 36 subjects), adverse event (13, 11.2%), withdrew consent (1, 0.9%), and other reasons (10, 8.6%). Of the 10 subjects who discontinued for other reasons, 7 subjects withdrew to undergo bone marrow/stem cell transplantation. The other 3 (of 10) subjects discontinued due to 1 each of: subject choice after achieving MRD negative CR: the need for long-term warfarin; and, deterioration secondary to diabetes mellitus. There were no differences in the reasons for discontinuation across dose cohorts for CLL/SLL subjects.

Major protocol violations/deviations

Protocol deviations were defined in accordance with the ICH guidelines and included, but were not limited to: inclusion/exclusion criteria violation, receipt of wrong treatment or incorrect dose of study drug, development of withdrawal criteria without being withdrawn, and use of prohibited concomitant medications. In addition, TLS prophylaxis and management deviations were also assessed. All deviations were assessed for impact on analyses and data integrity. Protocol deviations are summarised in Table 27.

None of the protocol deviations was considered to have affected the study outcome or interpretation of the study results or conclusions.

Table 27. Summary of Protocol Deviations

Protocol Deviation Categories	Number of Subjects N = 222
Inclusion/exclusion	11
Prohibited concomitant medications or food	19
Received incorrect dose	7
Treatment noncompliance	3
Failure to discontinue subjects	1
Other Good Clinical Practices	4
TLS Prophylaxis Deviation Categorised	**N = 60**
Guidelines pertaining to TLS prophylaxisd	20
Risk assessment not categorized appropriately	0
Dose not escalated properly	0
Uric acid reducer not administered for all doses	3
Not hospitalized when required	2
Intravenous hydration not administered	2
Chemistry panel not obtained	17

Baseline data

Demographic and other baseline characteristics of the 116 CLL/SLL subjects (102 CLL and 14 SLL) are presented in Table 28. The CLL/SLL study subjects were heavily pre-treated. A substantial proportion of subjects had CLL with risk factors for poor outcome (Table 29A). Subjects were classified in 3 categories based on the risk for developing TLS as defined by tumour burden and ALC (defined in Table 29B). TLS risk category was determined for 115 subjects: low for 28 (24.3%), medium for 47 (40.9%), and high for 40 (34.8%).

Table 28. Characteristics of the Patients at Baseline

Characteristic	Dose-Escalation Cohort (N = 56)	Expansion Cohort (N = 60)	All Patients (N = 116)
Age			
Median (range) — yr	67 (36–86)	66 (42–84)	66 (36–86)
≥ 70 yr — no. (%)	20 (36)	14 (23)	34 (29)
Sex — no. (%)			
Male	41 (73)	48 (80)	89 (77)
Female	15 (27)	12 (20)	27 (23)
Diagnosis — no. (%)			
Chronic lymphocytic leukaemia	49 (88)	53 (88)	102 (88)
Small lymphocytic lymphoma	7 (12)	7 (12)	14 (12)

Characteristic	Dose-Escalation Cohort (N = 56)	Expansion Cohort (N = 60)	All Patients (N = 116)
Rai stage III or IV — no. (%)	28 (50)	39 (65)	67 (58)
Median no. of previous therapies (range)[a]	4 (1–10)	3 (1–11)	3 (1–11)
Resistance to most recent therapy — no. (%)[b]	23 (41)	22 (37)	45 (39)
Previous fludarabine-based therapy — no. (%)			
Any previous fludarabine	51 (91)	49 (82)	100 (86)
Resistance to fludarabine	28 (50)	42 (70)	70 (60)
ECOG performance status — no. (%)			
Grade 0	29 (52)	27 (45)	56 (48)
Grade 1	27 (48)	31 (52)	58 (50)
Missing data	0	2 (3)	2 (2)

Table 29A. Characteristics of the Patients at Baseline

Characteristic	Dose-Escalation Cohort (N = 56)	Expansion Cohort (N = 60)	All Patients (N = 116)
Peripheral-blood lymphocytosis			
Absolute lymphocyte count > 5000 per mm^3 — no. (%)	31 (55)	35 (58)	66 (57)
Median count per mm3 (range)	27,600 (5400–204,500)	25,100 (5200–259,900)	27,500 (5200–259,900)
Bulky nodes — no. (%)			
> 5 cm	29 (52)	38 (63)	67 (58)
> 10 cm	10 (18)	12 (20)	22 (19)
Interphase cytogenetic abnormality — no./total no. with CLL (%)[c]			
Chromosome 17p deletion	19/49 (39)	12/53 (23)	31/102 (30)
Chromosome 11q deletion	13/49 (27)	15/53 (28)	28/102 (27)
No chromosome 17p or 11q deletion	16/49 (33)	27/53 (51)	43/102 (42)
Data missing or indeterminate	7/49 (14)	3/53 (6)	10/102 (10)
IGHV mutation status — no./total no. with CLL (%)			
Unmutated	26/49 (53)	20/53 (38)	46/102 (45)
Mutated	6/49 (12)	11/53 (21)	17/102 (17)
Data missing	17/49 (35)	22/53 (42)	39/102 (38)

aA total of 116 patients (100%) received anti-CD20 antibodies, 110 (95%) received alkylating agents, and 103 (89%) received purine analogues.bResistance was defined as either a lack of at least a partial response or disease progression while receiving therapy or within 6 months after the completion of therapy. Nineteen patients with resistance to fludarabine were also resistant to the combination of fludarabine, cyclophosphamide, and rituximab. cA total of 11 patients — 7 in the dose-escalation cohort and 4 in the expansion cohort — had both chromosome 17p and chromosome 11q deletions.

Table 29B. Summary of Protocol Deviations in the Main Cohort

Protocol Deviation Categories – Main Cohort			
Inclusion/exclusion	1		
Prohibited concomitant medication	15		
Incorrect dose of Venetoclax	2		
Treatment compliance	6		
Failure to discontinue subjects	1		
Other Good Clinical Practices	3		
Guidelines Pertaining to TLS Prophylaxis	Medically Significant	Not Medically Significant	Total
Risk assessment not categorized appropriately	0	0	0
Dose not escalated properly	7	0	7
Uric acid reducer not administered for all doses	2	15	17
Not hospitalized when required			
High Risk	5	0	5
Medium Risk (Creatinine Clearance < 80 mL/min)	0	25	25
Intravenous hydration not administered	4	6	10
Essential chemistry panel not obtained	32	18	50
Not obtained at Baseline	4	5	9
Not obtained at 6 hrs post dose or 8 hrs post dose	24	14	38
Not obtained at 24 hrs post dose	17	9	26

Results for efficacy outcomes

Investigator-assessed efficacy endpoints included ORR, duration of response, duration of PFS, EFS, OS, TTP, time to first response, time to 50% decrease in lymphocyte count, MRD assessment, and ECOG performance status.

The protocol allowed intra-subject dose escalations and de-escalations and small numbers of subjects were enrolled at certain dose levels.

In addition to the protocol-specified investigator assessments of efficacy, an independent review committee (IRC) evaluated tumour response and disease progression for all CLL subjects treated at 400 mg at the time of the interim analysis. The following efficacy endpoints were summarized based on this IRC review: ORR, CR rate, PR rate, duration of response, duration of PFS, and TTP.

Investigator Assessment of Efficacy Endpoints

Overall Response Rate per Investigator Assessment

Tumour response was evaluated in 56 subjects across 8 dose escalation cohorts and in 60 subjects in the safety expansion cohort (400 mg/day). Across the dose escalation cohorts with mean duration of venetoclax treatment of 19.1 months, ORR was 76.8% with 17 (30.4%) subjects achieving complete remission (CR/CRi), 2 (3.6%) achieving nodular PR status, and 24 (42.9%) achieving PR (Table 30). These results were similar across high-risk groups, including subjects with 17p deletion CLL, unmutated IGHV CLL, fludarabine-refractory CLL/SLL, and subjects with CLL bearing TP53 mutations and non-17p deletion as determined by exploratory analyses.

In the 400 mg safety expansion cohort of 60 subjects, duration of venetoclax treatment was shorter at a mean of 10.8 months. The ORR was 81.7%, with CR/CRi achieved by 5 (8.3%) subjects, PR by 42 subjects (70.0%), and nPR by 2 (3.3%) subjects. ORR was higher among CLL/SLL subjects treated in cohorts assigned to daily doses of 400 mg (82.1%) or higher (85.2%), as compared to subjects assigned to treatment with a daily dose below 400 mg (63.6%).

Table 30. Summary of Response – CLL/SLL Subjects

Number of Subjects (%), [95% CI][a]					
Subject Response[b]	Dose Escalation Cohorts N = 56	Safety Expansion Cohort N = 60	Dose Cohorts < 400 mg N = 22	Dose Cohorts = 400 mg N = 67	Dose Cohorts > 400 mg N = 27
Overall response rate (CR + CRi + nPR + PR)	43 (76.8) [63.6, 87.0]	49 (81.7) [69.6, 90.5]	14 (63.6) [40.7, 82.8]	55 (82.1) [70.8, 90.4]	23 (85.2) [66.3, 95.8]
Complete remission rate {CR + CRi}	17 (30.4) [18.8, 44.1] {13 + 4}	5 (8.3) [2.8, 18.4] {4 + 1}	3 (13.6) [2.9, 34.9] {3 + 0}	7 (10.4) [4.3, 20.3] {5 + 2}	12 (44.4) [25.5, 64.7] {9 + 3}
Nodular partial remission	2 (3.6)	2 (3.3)	0	2 (3.0)	2 (7.4)
Partial remission	24 (42.9)	42 (70.0)	11 (50.0)	46 (68.7)	9 (33.3)
Stable disease	9 (16.1)	9 (15.0)	7 (31.8)	9 (13.4)	2 (7.4)
Disease progression	0	1 (1.7)	0	1 (1.5)	0
Incomplete data[c]	4 (7.1)	1 (1.7)	1 (4.5)	2 (3.0)	2 (7.4)

CI = confidence interval; CR = complete remission; CRi = complete remission/incomplete bone marrow recovery; nPR = nodular partial remission; PR = partial remission. a) 95% CI is from the exact binomial distribution. b) For the investigator assessment, PR needs to be confirmed not less than 49 days apart. c) Includes subjects who discontinued prior to the first tumour assessment.

The median time to first achieve a PR was 1.4 months (range: 1.1 – 5.5 months) and the median time to achieve a CR or CRi was 5.6 months (2.8 – 19.4 months) for the dose

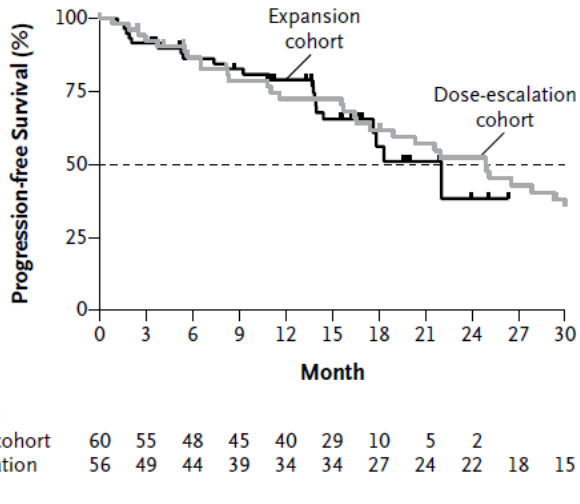
escalation cohorts. With continuing therapy beyond 12 months, 3 subjects improved their best response from PR to CR/Cri.

Progression-Free Survival

Median duration of PFS data could not be reliably estimated as of the interim data cut-off due to the relatively short follow-up time and the risk set from the safety expansion cohort being small past 12 months (< 20% of all subjects), resulting in potentially unstable estimates. The estimated proportion of subjects with PFS at 12 months was 72.5% (95% CI: 58.0, 82.8) in the dose escalation cohorts and 79.8% (66.1, 88.4) in the safety expansion cohort. Subjects in dose cohorts less than 400 mg have lower estimated 12 month PFS (58.4%) than those in 400 mg (81.8%) or higher dose cohorts (77.1%).

The Kaplan-Meier estimate for PFS is presented in Figure 17 for the dose escalation and safety expansion cohorts.

Figure 17. Proportions of patients with progression-free survival are shown for the dose-escalation and expansion cohorts.



IRC Assessment of Efficacy Endpoints

Overall Response Rate

At the time of the interim analysis, 57 CLL subjects had been treated at a 400 mg venetoclax dose and had response assessed by the IRC. There was a numerical difference in ORR between IRC assessment (73.7%) and investigators' assessments (80.7%) (Table 31). The ORR findings based on IRC were discordant with those based on investigators' assessment for 12 of the 57 subjects. The majority of discordant cases of best response between investigator and IRC assessment were a result of differences in CT assessments of lymph node sizes and/or non-target lesions.

Table 31. Summary of Response – IRC and Investigators' Assessments Among CLL Subjects Treated at 400 mg

Number of Subjects (%), [95% CI][a]		
Subject Response[b]	Assessed by IRC N = 57	Assessed by Investigatorsb N = 57
Overall response rate (CR + CRi + nPR + PR)	42 (73.7) [60.3, 84.5]	46 (80.7) [68.1, 90.0]

Number of Subjects (%), [95% CI][a]		
Complete remission rate {CR + CRi}	4 (7.0) [1.9, 17.0] {2 + 2}	7 (12.3) [5.1, 23.7] {5 + 2}
Nodular partial remission	0	2 (3.5)
Partial remission	38 (66.7)	37 (64.9)
Stable disease	NA	9 (15.8)
Disease progression	NA	1 (1.8)
Incomplete data	NA	1 (1.8)
Non-responder[c]	15 (26.3)	NA

CI = confidence interval; CR = complete remission; CRi = complete remission/incomplete bone marrow recovery; NA = not applicable; nPR = nodular partial remission; PR = partial remission. a) 95% CI is from the exact binomial distribution. b) For the investigator assessment, PR needed to be confirmed not less than 49 days apart. c) The non-responder response based on IRC assessments included responses of stable disease, progressive disease, and incomplete data based on investigators' assessments.

Progression-Free Survival

The estimated proportion of subjects with PFS at 12 months was similar between IRC and investigators' assessments (73.8% IRC versus 79.3% investigators).

Examination of Subgroups based on Investigator Assessments

Subgroup analyses were performed for investigator assessments of ORR, CR, and PR for all treated CLL/SLL subjects (Table 32).

Table 32. Complete and Overall Response Rates, According to Cohort and Subgroup.

Variable	No. of Patients	Complete Response Rate	Overall Response Rate
Age			
≥ 70 yr	34	21 (9–38)	71 (53–85)
< 70 yr	82	20 (12–30)	83 (73–90)
No. of previous therapies			
≥ 4	56	16 (8–28)	73 (60–84)
< 4	60	23 (13–36)	85 (73–93)
Fludarabine resistance			
Yes	70	16 (8–26)	79 (67–88)
No	44	27 (15–43)	82 (67–92)
Bulky nodes of > 5 cm			
Yes	67	8 (3–17)	78 (66–87)

Variable	No. of Patients	Complete Response Rate	Overall Response Rate
No	48	38 (24–53)	83 (70–93)
Chromosome 17p deletion			
Yes	31	16 (6–34)	71 (52–86)
No	60	18 (10–30)	80 (68–89)
Chromosome 11q deletion			
Yes	28	11 (2–28)	82 (63–94)
No	62	21 (12–33)	76 (63–86)
IGHV status			
Unmutated	46	17 (8–31)	76 (61–87)
Mutated	17	29 (10–56)	94 (71–100)

A total of 19 subjects with determined 17p deletion in the dose escalation cohorts and 12 such subjects in the 400 mg safety expansion cohort were evaluated for ORR. Albeit based on small numbers of subjects with 17p deletion, the ORR of 68.4% (13/19; 3 CR, 2 CRi, and 8 PR) for 17p deletion subjects in the dose escalation cohorts was similar to the ORR of 76.8% for all subjects in the dose escalation cohorts. Of the 12 subjects with 17p deletion in the safety expansion cohort, 9 subjects had partial remission and 3 had stable disease.

At the time of the interim analysis, 12 CLL subjects (from the 400 mg dose escalation cohort and 400 mg safety expansion cohort) with 17p deletion had been treated at 400 mg and had response assessed by the IRC. The ORR of 66.7% (8 [all PR]/12) based on IRC assessment was similar to the ORR of 75.0% (9 [all PR]/12) based on investigators' assessments of the same subjects.

7.1.2.2. Study M13-365: A Phase Ib Study Evaluating the Safety and Tolerability of Venetoclax (ABT-199) in Combination with Rituximab in Subjects with Relapsed Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Study design, objectives, locations and dates

This was a Phase Ib, open-label, multicenter study evaluating the safety and tolerability of venetoclax in combination with rituximab in up to 50 subjects with relapsed CLL or SLL.

Primary Objectives

The primary objectives of this study were to assess the safety profile, determine the maximum tolerated dose (MTD), and establish the Recommended Phase II Dose (RPTD) of venetoclax when administered in combination with rituximab in subjects with relapsed CLL or small lymphocyte leukaemia (SLL). The tolerability and the optimal lead-in period regimen of the combination were also determined.

Secondary Objectives

The secondary objectives of the study were to assess the pharmacokinetic profile and exploratory efficacy of the combination, including ORR, duration of response, and time to tumour progression (TTP).

Exploratory Objectives

The exploratory objectives of the study were to assess pharmacodynamics and pharmacogenetics of the combination and minimal residual disease (MRD) in the peripheral blood and bone marrow either by flow cytometry or real-time polymerase chain reaction (PCR).

Inclusion and exclusion criteria

Subjects were eligible for inclusion in this study if they met all of the following criteria:

- Subject was ≥ 18 years of age.
- Subject had a diagnosis of CLL/SLL that met published diagnostic criteria. Subjects had peripheral blood B-lymphocyte counts which clonally express CD5, CD19/20, and CD23 and were either kappa or lambda light chain restricted.
- Subject had relapsed CLL/SLL and met the following requirements:
    a. Received no more than 3 myelosuppressive treatment regimens for CLL/SLL. A full course of the same treatment regimen administered twice was counted as 2 regimens.
    b. Required treatment in the opinion of the investigator
- Subject had an ECOG performance score of ≤ 1.
- Subject had adequate bone marrow independent of growth factor support per local laboratory reference range at Screening as follows:
    a. Absolute neutrophil count (ANC) ≥ 1000/μL;
        i. An exception was for subjects with an ANC < 1000/μL and bone marrow heavily infiltrated with underlying disease (approximately 80% or more) may have used growth factor to achieve the ANC eligibility criteria per discussion with the AbbVie medical monitor;
    b. Platelets ≥ 50,000/mm3 (entry platelet count must have been independent of transfusion within 14 days of Screening)
    c. Haemoglobin ≥ 9.0 g/dL
- Subject had adequate coagulation, renal, and hepatic function, per laboratory reference range at Screening.
- Female subjects of childbearing potential and non-sterile male subjects must have practiced at least one of the following methods of birth control with partner(s) throughout the study and for 90 days after discontinuing study drug:
    a. Total abstinence from sexual intercourse as the preferred lifestyle of the subject; periodic abstinence was not acceptable;
    b. Surgically sterile partner(s); acceptable sterility surgeries are: vasectomy, bilateral tubal ligation, bilateral oophorectomy or hysterectomy;
    c. Intrauterine device;
    d. Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicidal jellies or cream AND a condom);
    e. Hormonal contraceptives (oral, parenteral, vaginal ring, or transdermal) for at least 3 months prior to study drug administration.

If hormonal contraceptives were used, the specific contraceptive must have been used for at least 3 months prior to study drug administration.

- Female of childbearing potential (that is, not postmenopausal for at least 2 years or surgically sterile) must have had negative results for pregnancy test performed.
- At Screening with a serum sample obtained within 14 days prior to the first study drug administration, and
- Prior to dosing on a urine sample obtained on the first day of study drug administration, if it had been > 7 days since obtaining the serum pregnancy test results.
- Subject voluntarily signed and dated an informed consent, approved by an IEC/IRB, prior to the initiation of any screening or study-specific procedures.
- Safety Expansion Cohort Only: Subjects with previous exposure to venetoclax were allowed ONLY in the dose escalation portion of the study.
- High risk CLL/SLL subjects required a pre-approval by the AbbVie medical monitor prior to enrolment.
- Male subjects must have refrained from sperm donation, from initial study drug administration until 90 days after the last dose of study drug.

Subjects were ineligible for this study if they met any one of the following criteria:

- CLL/SLL subject had undergone an allogeneic or autologous stem cell transplant.
- Subject had uncontrolled autoimmune hemolytic anaemia or thrombocytopenia.
- Subject had tested positive for human immunodeficiency virus (HIV).
- Seropositivity for hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) antibody or RNA. Note: Subjects with serologic evidence of prior vaccination to HBV (that is, anti-HBs+, anti-HBc–) may have participated.
- Subjects with a history of severe (defined as Grade 4 and/or requiring permanent discontinuation of prior antibody therapy) allergic or anaphylactic reactions to rituximab.
- Subject required the use of warfarin (due to potential drug-drug interactions that may potentially increase the exposure of warfarin and complications of this effect).
- Subject had received a live viral vaccine within 6 months prior to the first dose of study drug.
- Subject had received a monoclonal antibody for anti-neoplastic intent within 8 weeks prior to the first dose of study drug.
- Subject had received any of the following agents within 14 days prior to the first dose of study drug, or had not recovered to less than grade 2 clinically significant adverse effect(s)/toxicity(s) of the previous therapy:
    a. Any anti-cancer therapy including chemotherapy, immunotherapy, or radiotherapy;
    b. Investigational therapy, including targeted small molecule agents.
- Subject had received the following agents within 7 days prior to the first dose of study drug:
    a. Steroid therapy for anti-neoplastic intent;
    b. Cytochrome P450 (CYP) 3A inhibitors such as fluconazole, ketoconazole, and clarithromycin;
    c. Potent CYP3A inducers such as rifampin, carbamazepine, phenytoin, and St. John's wort.
- Subject had consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or Star fruit within 3 days prior to the first dose of study drug.

- Subject had a history of a prior significant toxicity, other than thrombocytopenia or neutropenia, from another Bcl-2 family protein inhibitor.
- Subject had a cardiovascular disability status of New York Heart Association Class ≥ 2. Class 2 is defined as cardiac disease in which subjects are comfortable at rest but ordinary physical activity, results in fatigue, palpitations, dyspnea or anginal pain.
- Subject had a significant history of renal, neurologic, psychiatric, pulmonary, endocrinologic, metabolic, immunologic, cardiovascular, or hepatic disease that in the opinion of the investigator would adversely affect his/her participating in this study. For subjects who required an intervention for any above diseases within the past 6 months, a discussion with the investigator and the AbbVie medical monitor occurred.
- A female subject who was pregnant or breast-feeding.
- Subject had a history of other active malignancies other than CLL within the past 2 years prior to study entry, with the exception of:
    a. Adequately treated in situ carcinoma of the cervix uteri;
    b. Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin;
    c. Previous malignancy confined and surgically resected (or treated with other modalities) with curative intent.
- Subject had malabsorption syndrome or other condition that precludes enteral route of administration.
- Subject exhibited evidence of other clinically significant ongoing or recent condition(s) including, but not limited to:
    a. Ongoing systemic infection (viral, bacterial, or fungal);
    b. Diagnosis of fever and neutropenia within 1 week prior to study drug administration.
- Safety Expansion Cohort Only: Subjects with previous exposure to venetoclax were not allowed in the safety expansion cohort portion of the study.

Study treatments

Venetoclax was administered once daily (beginning at 20 or 50 mg) and increased weekly to final cohort doses of 200, 300, 400, 500 or 600 mg/day, followed by rituximab given every 4 weeks for a total of 6 doses (first dose was 375 mg/m^2 and subsequent doses were 500 mg/m^2).

Efficacy variables and outcomes

Formal response assessment, including CT scan and bone marrow biopsy, was scheduled immediately after the end of combination therapy at 7 months. MRD was assessed on bone marrow aspirates in local laboratories using ≥ 4 colour flow cytometry with a minimum sensitivity of 0.01%.

Sample size

This was a dose escalation study. The number of subjects required was dependent upon the toxicities observed as the trial progressed, but it was expected that the dose escalation portion was to include approximately 30 subjects. Once the MTD was reached, up to 20 additional subjects were to be enrolled into expanded safety portion of this study at the RPTD and schedule of venetoclax.

Statistical methods

Descriptive statistics were provided for baseline demographic variables by dose and overall. Age, height, and weight were summarized with means, medians, standard deviations, and ranges. Frequencies and percentages were provided for gender and race.

The proportion of subjects with CR, complete remission with incomplete bone marrow (CRi), nodular partial remission (nPR), or partial remission (PR) based on a modified IWCLL updating of the NCI-WG 1996 guidelines were estimated and the corresponding 95% confidence interval for the proportion was constructed.

The objective response rate (CR/CRi or PR/nPR) was computed for all subjects (in the opinion of the investigator). The duration of overall response for a given subject was defined as the number of days from the day the criteria were met for CR/CRi or PR/nPR (whichever was recorded first) to the date that the earliest progressive disease was objectively documented. If a subject was still responding, then the subject's data were censored at the date of the subject's last visit at which an NCI-WG disease assessment was performed or at the cut-off date if that visit date was after the cut-off date. If a subject had progressive disease after the cut-off date, then the subject's data were censored at the date of the last NCI-WG disease assessment prior to the cut-off date. For subjects who never experienced response, the subjects' data were censored on the date of first dose. The analysis was not performed if the overall objective response rate was < 20%.

The distribution of the duration of overall response was estimated using Kaplan-Meier methodology for all dosed subjects. Median duration of response and the corresponding 95% confidence interval was estimated. Time to tumour progression for a given subject was defined as the number of days from the date the subject started study drug to the date that the earliest progressive disease was objectively documented. The distribution of the time to tumour progression was estimated using Kaplan-Meier methodology. Median time to tumour progression and the corresponding 95% confidence interval was estimated.

Enrolment of Subjects

As of the data cut-off, a total of 49 subjects were enrolled and received at least 1 dose of venetoclax.

Major protocol violations/deviations

A summary of protocol deviations identified in the study as of the data cut-off is presented in Table 33. None of the protocol deviations was considered to have affected the study outcome or interpretation of the study results or conclusions.

Table 33. Summary of Protocol Deviations

Protocol Deviation Categories	Number of Subjects (N = 49)
Inclusion/Exclusion	0
Prohibited Concomitant Medications	4
Failure to Discontinue Subjects	4
Treatment Compliance	2
Guidelines pertaining to TLS prophylaxis	
Risk assessment not categorized appropriately	0
Dose not escalated properly	0
Uric acid reducer not administered for all doses	1
Not hospitalized when required	1
Intravenous hydration not administered	1
Essential chemistry panel not obtainede	9

Protocol Deviation Categories	Number of Subjects (N = 49)
Other Good Clinical Practices	

Baseline data

Of the 49 subjects, the majority were male (61.2%), white (98.0%), ≥ 65 years of age (57.1%) (range 50 – 88 years), and treated in the United States (67.3%). The median number of prior therapies was 2 (range 1 – 5). 19.6% (9 of 46) had 17p deletion. The majority of subjects had additional high risk features of disease: 70.4% (19 of 27) were IGVH unmutated; 32.1% (9 of 28) were refractory to fludarabine; 44.9% (22 of 49) had a lymph node ≥ 5 cm; and 44.9% (22 of 49) had an ALC ≥ 25 × 10^9/L. The median time on study was 10.3 months (range 0.03 – 27.6 months). Of the 49 CLL/SLL subjects, 79.6% were still active on study at the data cut-off.

Results for efficacy outcomes

Tumour response was evaluated by the investigator in all 49 subjects across all dose cohorts (Table 34). The ORR was 81.6%, the CR rate was 36.7% and the deep response rate (CR + CRi + nPR) was 40.8%. The responses were rapid, with a median time to first response of 2.8 months (range 1.1 – 3.8) and a median time to CR of 7.5 months (range 6.4 – 14.0). The time to response was longer compared to the monotherapy studies, but this was a function of the study visit schedule, with the first response assessment required at 2 – 3 months and a bone marrow biopsy to document CR status at 7 months. Among subjects continuing venetoclax as a single agent following the combination period, 7 of 18 (38.9%) subjects attained CR after the mandated assessment at 7 months. Sixteen subjects received 400 mg of venetoclax (8 during dose escalation and 8 during cohort expansion). For these 16 subjects, the response rates were similar as the overall population (ORR 81.2%, CR rate 37.5% and deep response rate 37.5%).

Table 34. Responses in R/R CLL Subjects for Study M13-365 (Investigator Assessed)

Subject Response[a]	Total N = 49 % (n) [95% CI]	Cohort 3 N = 8 (400 mg) % (n) [95% CI]	Cohort 6 N = 8 (400 mg SE) % (n) [95% CI]
Objective response rate (CR + CRi + nPR + PR)	81.6 (40) [68.0, 91.2]	75.0 (6) [34.9, 96.8]	87.5 (7) [47.3, 99.7]
Complete remission rate (CR + CRi)	36.7 (18) [23.4, 51.7]	50.0 (4) [15.7, 84.3]	25.0 (2) [3.2, 65.1]
Nodular partial remissiona	4.1 (2)	0	0
Partial remission	40.8 (20)	25.0 (2)	62.5 (5)
Stable disease	12.2 (6)	12.5 (1)	0
Disease progression	4.1 (2)	0	12.5 (1)
Incomplete data	2.0 (1)	12.5 (1)	0

•CI = confidence interval (95% CI is from the exact binomial distribution); CR = complete remission; CRi = complete remission with incomplete marrow recovery; PR = partial remission; SD = stable disease; SE = safety expansion. a) PR needs to be confirmed not less than 49 days apart for objective response.

Of the 18 subjects who achieved CR, 5 subsequently discontinued venetoclax (none had 17p deletion). All of these subjects are continuing with study follow-up every 12 weeks (ranging from 6.8 – 19.1 months since discontinuing venetoclax) and none have had evidence of clinical

disease progression, demonstrating the durability of response, even in the absence of continuous therapy.

MRD analysis was an exploratory objective for all subjects enrolled with a mandated assessment at the 7-month mark. Subjects treated with the combination of venetoclax and rituximab had a 44.9% (22/49) MRD-negative rate in the bone marrow in an intent-to-treat analysis. This included 11 of 18 subjects (61.1%) who achieved CR and 10 of 22 subjects (45.5%) who achieved PR.

The estimated proportion of subjects with a durable response at 12 months was 93.1% and the median duration of response had not been reached. The Kaplan-Meier estimate for subjects without progression at 12 months was 88.7% and the median time to progression had not been reached.

Subgroup analysis was performed for subjects with 17p deletion (n = 9) and showed that the ORR was 66.7%, the CR rate was 22.2%, and the MRD-negativity rate in bone marrow was 44.4%. Two subjects with 17p deletions received 400 mg of venetoclax and the response was PR for one subject and incomplete data for the other. The estimated proportion of 17p del subjects with a durable response at 12 months was 83.3% (5 of 6 subjects) and the estimate proportion without progression at 12 months was 100.0%.

7.1.2.3. Study M14-032: A Phase II Open-Label Study of the Efficacy and Safety of Venetoclax (ABT-199/GDC-0199) in Chronic Lymphocytic Leukemia Subjects with Relapse or Refractory to B-Cell Receptor Signalling Pathway Inhibitor Therapy

Study design, objectives, locations and dates

An open-label, non-randomised, uncontrolled, 2-arm, multi-centre, Phase II study evaluating 400 mg of venetoclax in subjects with CLL who have failed (defined as progression during treatment or after discontinuation) either ibrutinib or idelalisib.

Objectives

The primary objective of this study was to evaluate the efficacy and safety of venetoclax monotherapy in subjects with chronic lymphocytic leukaemia (CLL) relapsed after or refractory to treatment with B-cell receptor signalling pathway inhibitors. Efficacy was measured by overall response rate (ORR).

Inclusion and exclusion criteria

Eligible subjects were considered for inclusion in this study if they met all of the following criteria:

Subjects with relapsed or refractory CLL were selected to participate in this study. Subjects must have relapsed or be refractory to ibrutinib- or idelalisib-containing regimen. A subject was eligible for study participation if he/she met the following criteria:

- Subject had a diagnosis of CLL that met published 2008 International Workshop on Chronic Lymphocytic Leukemia National Cancer Institute-sponsored Working Group (IWCLL NCI-WG) criteria. 2. Subject had R/R disease with an indication for treatment according to the 2008 IWCLL NCI-WG criteria.
- Subject had refractory disease or developed recurrence after therapy with either ibrutinib or idelalisib and met 1 of the following:
    a. Treatment failure with either of the above agents;
    b. Progression during treatment or after discontinuation of either of the above agents.
- Subject had adequate bone marrow function at Screening as follows:

a. Absolute Neutrophil Count (ANC) ≥ 1000/µL;

   i. An exception was for subjects with an ANC < 1000/µL at Screening; when bone marrow is heavily infiltrated with underlying disease (approximately 80% or more), granulocyte-colony stimulating factor (G-CSF) may have been administered at the discretion of the investigator, after Screening and prior to the first dose of venetoclax to achieve the ANC eligibility criteria (≥ 1000/µL).

b. Platelets ≥ 30,000/mm3 (without transfusion support, evidence of mucosal bleeding, known history of bleeding episode within 3 months of screening and history of bleeding disorder);

c. Haemoglobin ≥ 8.0 g/dL

   i. For subjects with autoimmune hemolytic anaemia or idiopathic thrombocytopenic purpura, haemoglobin of < 8 g/dL and platelet count of < 30,000/mm^3 without corticosteroid therapy, a discussion between the investigator and the AbbVie medical monitor must occur.

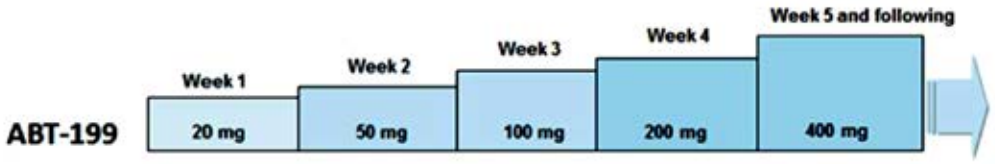
Subjects were not eligible for this study if they met any of the following criteria:

- Subject had previously received venetoclax.
- Subject had undergone an allogeneic stem cell transplant within the past 1 year.
- Subject had developed Richter's transformation confirmed by biopsy.
- Subject had active and uncontrolled autoimmune cytopenias (for 2 weeks prior to screening), including autoimmune hemolytic anaemia and idiopathic thrombocytopenic purpura despite low-dose corticosteroids.
- Subject had chronic hepatitis B virus (HBV) or hepatitis C (HCV) requiring treatment. Note: Subjects with serologic evidence of prior vaccination to HBV (that is, hepatitis B surface antigen [HBs Ag]–, anti-HBs+ and anti-hepatitis B core antigen [HBc]–) and positive anti-HBc from intravenous immune globulin (IVIG) may have participated.
- Subject had known contraindication or allergy to both xanthine oxidase inhibitors and rasburicase.
- Subject had malabsorption syndrome or other condition that precludes enteral route of administration.
- Subject had unresolved toxicities from prior anti-cancer therapy, defined as any grade 2 or higher clinically significant non-hematologic toxicity (excluding alopecia).

Study treatments

Venetoclax was administered orally once daily (QD), continuously. To mitigate the risk for tumour lysis syndrome (TLS), a lead-in (ramp-up) period of 5 weeks was employed with step-wise dose increments to facilitate gradual debulking (Figure 18).

Figure 18. Dosing Schematic



Efficacy variables and outcomes

The primary objective of this study was to evaluate the efficacy and safety of venetoclax monotherapy in subjects with chronic lymphocytic leukaemia (CLL) relapsed after or refractory

to treatment with B-cell receptor signalling pathway inhibitors. Efficacy was measured by overall response rate (ORR).

For disease assessments, response was assessed by the investigator based on analysis of clinical laboratory tests (haematology laboratory values), complete physical examination, CT scan of involved anatomic regions (or magnetic resonance imaging [MRI] if CT was medically contraindicated), bone marrow aspirate and biopsy. Subjects were evaluated against the 2008 Modified IWCLL NCI-WG Criteria for Tumour Response with the addition of CT imaging (or MRI).

Sample size

There were no planned hypotheses testing on the primary endpoint ORR. ORR was presented by a point estimate and its corresponding 95% confidence interval. A sample size of 20 subjects would ensure that the distance of true rate was within 23% of the observed rate with 95% confidence and a sample size of 40 subjects would ensure that the distance of true rate will be within 17% of the observed rate with 95% confidence.

Statistical methods

Overall Response Rate

The proportion of subjects with overall response (per the investigator assessment) was calculated for all subjects based on IWCLL NCI-CWG criteria. In addition, a 95% confidence interval based on binomial distribution was constructed for the calculated ORR.

Enrolment of Subjects

As of the data cut-off of 30 April 2015, a total of 28 subjects were enrolled and received at least 1 dose of venetoclax.

Major protocol violations/deviations

Protocol deviations were defined in accordance with the International Conference on Harmonisation (ICH) guidelines. In addition, TLS prophylaxis and management deviations were also assessed. All deviations were assessed for impact on analyses and data integrity. None of the protocol deviations were considered to have affected the study outcome or interpretation of the study results or conclusions. A summary of protocol deviations identified in the study as of the data cut-off is presented in Table 35.

Table 35. Protocol deviations

Protocol Deviation Categories	Number of Subjects (N = 28)
Inclusion/Exclusion	0
Prohibited Concomitant Medications	1
Failure to Discontinue Subjects	0
Treatment Compliance	0
Guidelines pertaining to TLS prophylaxis	
Risk assessment not categorized appropriately	1
Dose not escalated properly	1
Uric acid reducer not administered for all doses	0
Not hospitalized when required	0
Intravenous hydration not administered	0

Protocol Deviation Categories	Number of Subjects (N = 28)
Essential chemistry panel not obtainede	12
Other Good Clinical Practices	0

Baseline data

As of the data cut-off of 30 April 2015, a total of 28 subjects were enrolled and received at least 1 dose of venetoclax at 8 sites in the United States. The majority of subjects enrolled in the study were white (96.4%) and male (78.6%). The median number of prior oncology medications was 5 (range 1 to 12). The subjects ranged in age from 50 to 75 years of age (median: 66 years). 32.1% (9 of 28) of subjects had 17p deletion, and 28.6% (8 of 28) had a TP53 mutation, all of whom also had 17p deletion. The majority of subjects had additional high risk features of disease: 7.1% of subjects were ≥ 75 years of age; 80.0% (16 of 20) were IGVH unmutated; 50.0% (14 of 28) had a lymph node > 5 cm; and 25.0% (7 of 28) had an ALC ≥ 25 × 109/L. As of the data cut-off, 5 subjects have discontinued the study, 3 due to disease progression, 1 because of a non-fatal event of respiratory failure, and 1 reported death due to unknown cause. Median time on study was 2.3 months (range 0.1 – 7.0).

Results for efficacy outcomes

Preliminary Efficacy in Subjects who Previously Failed Ibrutinib

In this document, the efficacy data as determined by the investigator were provided. Of the 22 subjects in Arm A, 15 had completed the first response assessment at 8 weeks, with results of PR (53.3%), SD (40.0%) and not evaluable (6.7%) due to baseline disease burden in the bone marrow only. Of these 15 subjects, one, who had a confirmed PR at Week 24, developed progression due to Richter's transformation at Week 29. All others remain on study.

Preliminary Efficacy in Subjects who Previously Failed Idelalisib

Of the 6 subjects in Arm B, 4 had completed the first response assessment at 8 weeks, with results of PR (50.0%), SD (25.0%) and PD (25.0%). In total, 10 of 19 (52.6%) evaluable subjects had a response of PR. Eight of the PRs have not been confirmed per IWCLL criteria as of yet, due to having been enrolled only recently. Nevertheless, even at this early assessment point, the fact that so many of these patients are responding and remain on study suggests that venetoclax may have a crucial role in the treatment of CLL patients who have relapsed or are or refractory to therapy with BCR inhibitors.

7.1.3. Evaluator's conclusions on clinical efficacy

For the treatment of patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy; this includes patients with 17p deletion, the sponsors have provided one pivotal Phase II single arm study in R/R CLL subjects harbouring 17p deletion, supported by one Phase I single arm, dose-escalation study, which includes R/R CLL and SLL subjects. Two additional supportive studies were provided: Study M14-032, a Phase II, two-arm study, which provided preliminary evidence of venetoclax monotherapy activity in subjects who were refractory to ibrutinib or idelalisib; and Study M13-365, a Phase Ib one-arm study of the safety and tolerability of venetoclax in combination with rituximab in subjects with relapsed CLL/SLL. The efficacy data from Study M13-365 were not included in the monotherapy pooled analysis.

The sponsor has satisfactorily demonstrated that venetoclax monotherapy is effective in relapsed/refractory CLL, achieving ORRs of between 73% (M12-175) and 79% (M13-982) across molecular prognostic groups and 12 month PFS estimated at 72%. In addition, data has been presented which shows venetoclax is safe when combined with rituximab (M13-365). Moreover, in patients with R/R CLL and abnormalities of chromosome 17p, ORR with venetoclax was 79% compared to previous ORRs of 29% to 35% after standard fludaradine-

based regimens.[1,2] However, the durability of remissions, measured by progression-free survival, and the impact of venetoclax therapy on overall survival have not been defined. The sponsor has used Overall Response Rate (ORR) as a surrogate endpoint for PFS and OS. Measuring ORR has the advantage of allowing effect to be attributed to venetoclax and not the natural history of R/R CLL, but is not a comprehensive measure of activity and has not been directly validated in CLL studies.

To justify the use of ORR, the sponsors have referenced Badoux 2011[1], however this study reported associations with CR and nPR not ORR, which includes CR + CRi + nPR + PR. In this study of FCR for the treatment of R/R CLL, 'superior outcomes for time-to-event endpoints were observed for patients who achieved CR or nPR', with estimated median PFS for patients achieving CR 60 months compared with 38 months for patients achieving nPR (P =0.076) and 15 months for those achieving PR (P <0.001); and TTP was associated with MRD status by flow cytometry for patients achieving CR. However, there was no significant difference in OS for patients achieving CR or flow MRD–negative status and there were no differences in TTP or OS according to flow or PCR MRD status in patients whose best responses were PR or nPR.[1] In Tam 2008[3], CR was associated with OS in FCR-treated R/R CLL. Patients in CR had the most favourable TTP (median: 85 months) and survival (88% at 6 years), followed by patients in nodular partial response (PR-nod) who had a shorter TTP (median: 71 months, P = .03) but similar survival (77% at 6 years, P =0.12). Compared with PR-nod, patients in CR except for incomplete recovery of blood counts (PR-i) had similar TTP (median: 50 months, P =0.28), but experienced shorter survival (42% at 5 years, P =0.01).

ORR has been used as a surrogate for accelerated approval of venetoclax by the FDA for the treatment of patients with chronic lymphocytic leukaemia with 17p deletion. However, in addition to the effect size of venetoclax and the limited benefits of other available therapies, or effect duration, ideally justification of the use of ORR as a surrogate end-point should be established by the sponsor.

In the submitted proposal, evidence of efficacy was presented by the sponsor for (1) patients with TP53 aberrations and/or (2) those with refractory or relapsed CLL. It was therefore considered that the proposed indication: 'Venclexta is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy; this includes patients with 17p deletion', was too broad and did not define a relapsed/refractory CLL group. Furthermore, although evidence of efficacy in R/R CLL with 17p deletion had been provided, evidence of efficacy for the treatment of all patients with CLL who had received at least one prior therapy was not satisfactorily demonstrated. For each of the provided studies for efficacy, the specifically targeted CLL groups are detailed as follows:

7.1.3.1. Pivotal Study M13-982

- Targeted to subjects harbouring the 17p deletion.
- Refractory or had relapsed after receiving at least 1 prior line of therapy (subjects that progressed after 1 cycle of treatment [safety expansion cohort] or had completed at least 2 cycles of treatment for a given line of therapy.
- In the safety-expansion cohort, previously untreated CLL subjects harbouring the 17p deletion.
- Specifically excluded: subjects who had undergone an allogeneic stem cell transplant, developed Richter's transformation, active and uncontrolled autoimmune cytopenias (2 weeks prior to Screening), and subjects with prolymphocytic leukaemia (safety expansion cohort only, efficacy not assessed for interim report)

7.1.3.2. Study M12-175

- Subjects had relapsed following or were refractory to standard treatments such as fludarabine-based regimens (F, FC, FR or FCR) or alkylator (chlorambucil, bendamustine) based regimens.

7.1.3.3. Study M14-032

- Subjects with chronic lymphocytic leukaemia (CLL) relapsed after or refractory to treatment with B-cell receptor signalling pathway inhibitors.

7.1.3.4. Study M13-365

- Subjects with relapsed CLL or SLL.

With regard to the 3 studies which included CLL subjects negative for the 17p deletion, the Sponsor has not provided satisfactory evidence of efficacy as detailed below:

7.1.3.5. Study M12-175

The primary objectives of this study were to assess the safety profile, characterise pharmacokinetics, determine the MTD, determine the recommended Phase II dose (RPTD), including the ramp-up period regimen of venetoclax. All efficacy analyses were exploratory in nature.

7.1.3.6. Study M14-032

The primary objective of this study was to evaluate the efficacy and safety of venetoclax monotherapy in subjects with CLL relapsed after or refractory to treatment with B-cell receptor signalling pathway inhibitors. However, there were no planned hypotheses testing on the primary endpoint ORR criteria and numbers of subjects analysed were low (15 in the ibrutinib group and 4 in the idelalisib group).

7.1.4. Study M13-365

The primary objectives of this study were to assess the safety profile, determine the MTD, and establish the RPTD of venetoclax when administered in combination with rituximab. Efficacy analyses in this study were exploratory.

Although the datasets are immature, venetoclax does show activity across molecular prognostic groups, and it is expected that the indication will expand to include R/R subjects without 17p deletion.

Within the ORR groups in each study, it was noted that CR was infrequent. However, it was considered that in clinical practice venetoclax would be used concurrently with chemotherapy and immunotherapy regimens. The safety, and early evidence of efficacy of venetoclax in combination with rituximab was presented in Study M13-365 and the results of a Phase III study (NCT02005471), which will compare the efficacy of venetoclax plus rituximab with bendamustine plus rituximab in patients with relapsed or resistant chronic lymphocytic leukaemia are awaited.

8. Clinical safety

Two important risks, tumour lysis syndrome (TLS) and neutropenia were identified when treating R/R CLL. Both of these risks are consistent with a Bcl-2 mechanism based toxicity in the CLL setting:

- TLS: The risk of TLS with venetoclax is a result of on-target effects and rapid reduction of tumour volume. The risk is during the first 5 weeks of treatment. A low starting dose followed by gradual dose ramp-up allowed for the tumour size to be gradually reduced and

was effective in reducing the risk of TLS. Tumour lysis syndrome can be managed following standard of care guidelines.

- Neutropenia: Neutropenia generally resolved with standard of care measures, few events were serious, and no events led to discontinuation of venetoclax. An apparent correlation with increased rate of infection was not found.

8.1. Studies providing evaluable safety data

The overall clinical safety evaluation of venetoclax for the treatment of CLL included a total of 553 subjects who received at least 1 dose of venetoclax. This safety population included 289 subjects with CLL treated with venetoclax monotherapy, 88 subjects with CLL treated with venetoclax combination therapy, 106 subjects with non-Hodgkin's lymphoma (NHL) treated with venetoclax monotherapy, and 70 subjects from relevant pharmacology studies (12 NHL subjects and 58 healthy subjects).

The venetoclax monotherapy studies in CLL include 1 pivotal study and 2 key supportive ongoing clinical studies:

- Pivotal Study M13-982 in subjects with R/R or previously untreated CLL harbouring the 17p deletion (N = 145, 400 mg dose).
- Key supportive Study M12-175 evaluated multiple dose levels of venetoclax in subjects with R/R CLL (Arm A) (N = 116 [67 subjects at 400 mg dose]).
- Key supportive Study M14-032 in subjects with CLL that was R/R to ibrutinib or idelalisib treatment (N = 28, 400 mg dose).
- The 3 ongoing venetoclax combination therapy studies listed below provided supportive safety data:
- Study M13-365 evaluated venetoclax + rituximab in subjects with relapsed CLL (N = 49)
- Study GO28440 evaluated venetoclax + bendamustine/rituximab (BR) in subjects with R/R or previously untreated CLL (N = 19).
- Study GP28331 evaluated venetoclax + obinutuzumab in subjects with R/R or previously untreated CLL (N = 20).

8.1.1. Pivotal efficacy study

In the main cohort of the pivotal study, safety and tolerability of venetoclax in subjects with relapsed or refractory CLL harbouring 17p deletion was a secondary objective.

The primary objective of the safety expansion cohort was to evaluate the safety of venetoclax in approximately 50 subjects with relapsed/refractory or previously untreated CLL harbouring 17p deletion treated per an updated TLS prophylaxis and management measures.

The safety assessments included the following and were reported for drug-related AEs and regardless of causality:

- Frequency of on-study AEs and on-study serious AEs [SAE]
- Frequency of on-study AEs and on-study SAEs leading to discontinuation
- Frequency of AEs of special interest
- Frequency of deaths
- Laboratory assessments for safety, including haematology, liver parameters, renal/electrolyte parameters
- Electrocardiograms (ECG)

· Vital signs and physical measurements

8.1.1.1. Safety evaluation

In this interim report, safety was assessed in 145 subjects who started treatment prior to (or on) 26 March 2015 and therefore had the opportunity to complete the 5-week ramp-up period; 107 subjects in the main cohort and 38 subjects in the safety expansion cohort. The data cut-off date for this interim report was 30 April 2015. At the time of the data cut-off, 2 subjects with previously untreated CLL were enrolled in the safety expansion cohort and were included in the overall safety analysis.

As of the data cut-off date for this interim CSR (30 April 2015), a majority of subjects (75/145; 51.7%) had received venetoclax for > 48 weeks; all of these subjects were in the main cohort. In the safety expansion cohort, all subjects but 2 completed the ramp-up period and the majority had received venetoclax for > 12 weeks; no subject in the safety expansion cohort has received venetoclax for > 32 weeks.

To mitigate the risk of TLS, a modified lead-in period was implemented starting from Protocol Amendment 1 with a venetoclax starting dose of 20 mg and gradual weekly dose increase (4 or 5 weeks in Protocol Amendment 1; 5 weeks in Protocol Amendments 2 and 3) to the final dose of 400 mg.

An overview of treatment-emergent adverse events is reported in Table 36.

Table 36. Overview of Treatment-Emergent Adverse Events and All Deaths – All Treated Subjects

Adverse Event Category	Main Cohort (N = 107) n (%)	Safety Expansion Cohort (N = 38) n (%)	Total (N = 145) n (%)
Any AE	103 (96.3)	38 (100)	141 (97.2)
Any AE with NCI-CTCAE grade ≥ 3	81 (75.7)	19 (50.0)	100 (69.0)
Any AE with NCI-CTCAE Grade 3 or 4	81 (75.7)	19 (50.0)	100 (69.0)
Any AE with a reasonable possibly of being related to venetoclax[a]	90 (84.1)	31 (81.6)	121 (83.4)
Any SAE	59 (55.1)	12 (31.6)	71 (49.0)
Any AE leading to study discontinuation	19 (17.8)	1 (2.6)	20 (13.8)
Any AE leading to venetoclax discontinuation[b]	20 (18.7)	1 (2.6)	21 (14.5)
Any AE leading to venetoclax discontinuation – disease progression	11 (10.3)	0	11 (7.6)
Any AE leading to venetoclax discontinuation – not disease progression	9 (8.4)	1 (2.6)	10 (6.9)
Any AE leading to venetoclax interruption	36 (33.6)	9 (23.7)	45 (31.0)

Adverse Event Category	Main Cohort (N = 107) n (%)	Safety Expansion Cohort (N = 38) n (%)	Total (N = 145) n (%)
Any AE leading to venetoclax reduction	13 (12.1)	4 (10.5)	17 (11.7)
Any fatal AE	12 (11.2)	0	12 (8.3)
Deaths	11 (10.3)	0	11 (7.6)

AE = adverse event; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SAE = serious adverse event. a) As assessed by the investigator. b) A total of 12 subjects had an adverse event listed as the primary reason for venetoclax discontinuation; 21 subjects had adverse events leading to venetoclax discontinuation. c) Deaths occurred within 30 days from last dose of venetoclax. Total includes a subject who experienced an AE that resulted in death after the data cut-off date of 30 April 2015. Seven additional subjects died as a result of disease progression after > 30 days from last dose of venetoclax.

Treatment-emergent AEs were experienced by 141 subjects (97.2%). The most commonly reported (> 15% subjects) AEs, regardless of relationship to study drug or severity, were neutropenia (39.3%), nausea (29.7%), diarrhoea (29.0%), anaemia (25.5%), fatigue (19.3%), thrombocytopenia (17.2%) and pyrexia (15.9%).

Of note, autoimmune hemolytic anaemia was reported in 6.9% of all subjects and immune thrombocytopenic purpura in 3.4%. This is not unexpected given the underlying disease process. In general, the incidence of AEs was lower in the safety expansion cohort than the main cohort, which likely reflects the shorter duration of venetoclax treatment in the expansion cohort.

The SOCs in which subjects most commonly reported AEs were Infection and Infestations (64.1%), Gastrointestinal Disorders (62.1%) and Blood and Lymphatic System Disorders (56.6%).

Treatment-emergent AEs assessed by the investigator as having a reasonable possibility of being related to venetoclax were experienced by 121 subjects (83.4%). The most commonly reported related AEs were neutropenia (31.0%) and nausea (20.7%). Related AEs were most commonly reported in the SOCs of Blood and Lymphatic System Disorders (39.3%) and Gastrointestinal Disorders (35.2%).

Toxic effects that were reported during venetoclax therapy in all 145 patients are summarised in Table 37 and 38.

Table 37. Treatment-Emergent Adverse Events with a Reasonable Possibility of Being Related to Study Drug in ≥ 5% of All Treated Subjects and by System Organ Class

Adverse event	Total (N = 145) n (%)
Anaemia	16 (11.0)
Neutropenia	45 (31.0)
Thrombocytopenia	14 (9.7)
Diarrhoea	20 (13.8)
Nausea	30 (20.7)
Fatigue	18 (12.4)

Adverse event	Total (N = 145) n (%)
Pyrexia	12 (8.3)
Hyperkalaemia	8 (5.5)
Hyperphosphataemia	16 (11.0)
Tumour lysis syndrome	8 (5.5)
Infections and Infestations	25 (17.2)
Musculoskeletal and Connective Tissue Disorders	9 (6.2)
Nervous System Disorders	12 (8.3)
Skin and Subcutaneous Tissue Disorders	19 (13.1)

Table 38. Treatment-Emergent Grade 3 or 4 Adverse Events in ≥ 2% of All Treated Subjects and by System Organ Class

Adverse event	Total (N = 145) n (%)
Anaemia	23 (15.9)
Autoimmune haemolytic anaemia	8 (5.5)
Febrile neutropenia	8 (5.5)
Immune thrombocytopenic purpura	5 (3.4)
Leukopenia	6 (4.1)
Neutropenia	54 (37.2)
Thrombocytopenia	19 (13.1)
Cardiac Disorders	4 (2.8)
Gastrointestinal Disorders	10 (6.9)
General Disorders and Administration Site Conditions	6 (4.1)
Hepatobiliary Disorders	3 (2.1)
Infections and Infestations	24 (16.6)
Pneumonia	6 (4.1)
Injury, Poisoning and Procedural Complications	3 (2.1)
Hypokalaemia	3 (2.1)
Hypophosphataemia	4 (2.8)
Tumour lysis syndrome	8 (5.5)
Musculoskeletal and Connective Tissue	7 (4.8)
Neoplasms Benign, Malignant and Unspecified (incl. cysts and polyps)	12 (8.3)
Malignant neoplasm progression	3 (2.1)
Nervous System Disorders	5 (3.4)
Respiratory, Thoracic and Mediastinal	4 (2.8)

Adverse event	Total (N = 145) n (%)
Vascular Disorders	7 (4.8)
Hypertension	4 (2.8)

8.2. Key Supportive Monotherapy Studies in CLL

Studies included in Module 5 that assessed safety as a primary outcome were studies CA204005, CA204010, and HuLuc63-1701. PK studies in renal failure were included in Study CA204007 and ECG changes were a primary outcome in the biomarker study, HuLuc63-1701.

8.2.1. Study M12-175 (Arm A)

Study M12-175 is a Phase I, first-in-human, open-label, multicenter study evaluating the safety and pharmacokinetic profile of venetoclax under a QD dosing schedule in 116 subjects with R/R CLL in Arm A. The study comprised Dose Escalation Cohorts followed by an Expanded Safety Cohort, as described below. Study enrolment has been completed and the study is ongoing.

- Dose Escalation Cohorts (N = 56): Subjects were enrolled to define the dose limiting toxicities (DLTs) and maximum tolerated dose (MTD).
- Expanded Safety Cohort (N = 60): Subjects were enrolled at the recommended Phase II dose (RPTD) and schedule.

During the dose escalation portion of the study, venetoclax dosing escalated up to 1200 mg QD following a ramp-up dosing schedule that started with Amendment 3 (Cohort 2). The RPTD was determined to be 400 mg QD for CLL, and all subjects in the Expanded Safety Cohort received venetoclax following the dosing regimen shown in Figure 15.

8.2.1.1. Safety evaluation

Almost all CLL/SLL subjects (99.1%, 115/116) experienced at least 1 treatment-emergent adverse event. The 3 most common adverse events, regardless of grade, reported for CLL/SLL subjects, irrespective of severity or relationship to study drug, included diarrhoea (49.1%), nausea (47.4%), and neutropenia (44.8%). Adverse events that were NCI CTCAE Grade 3 or 4 were reported for 93 (80.2%) CLL/SLL subjects, 41 of who had a Grade 4 event. The incidence of any Grade 3 or 4 adverse event was 81.7% (49/60) in the safety expansion cohort and 71.4% to 80.0% among subjects treated at higher daily doses (600 mg to 1200 mg). The 3 most common Grade 3 or 4 adverse events were neutropenia (41.4%), anaemia (12.1%), and thrombocytopenia (12.1%). Nine subjects experienced adverse events categorized as DLTs, 6 during the dose escalation period (that is, during the ramp-up period plus 3 weeks at the designated cohort dose, per protocol) and 3 after the dose escalation period.

The adverse event profile of venetoclax, based on type and severity, in patients with 17p deletion was similar to that of all treated CLL/SLL population.

Treatment-emergent serious adverse events were reported in 48 (41.4%) of all CLL/SLL subjects as of the data cut-off for this interim CSR. Serious adverse events reported for > 2 subjects, regardless of relationship to study drug, were febrile neutropenia for 7 subjects (6.0%) and immune thrombocytopenia purpura, pneumonia and TLS for 3 subjects each (2.6%).

As of the data cut-off, 18 CLL/SLL subjects had died; 5 subjects within 30 days of the last dose of study drug and 13 subjects more than 30 days after the last dose of study drug. According to the investigators, 12 of these subjects died due to disease progression that was not reported as an adverse event. Six (5.2%) subjects experienced an adverse event that resulted in their death, 5 subjects within 30 days of the last dose of study drug (that is, 2 due to an event of malignant neoplasm progression and 1 each due to multi-organ failure, small intestinal obstruction, viral

pneumonia, and sudden death in the setting of TLS) and 1 subject > 30 days after the last dose of study drug (due to an event of viral pneumonia).

Sixteen (13.8%) and 37 (31.9%) of subjects had events led to discontinuation of venetoclax and venetoclax interruption, respectively. Thrombocytopenia (3 subjects, 2.6%) was the only adverse event leading to venetoclax discontinuation for more than 1 subject.

Tumour lysis syndrome, neutropenia (including febrile neutropenia) ≥ Grade 3, infections ≥ Grade 3, and second primary malignancy (excluding non-melanoma skin cancers) were adverse events of special interest (AESI) that were closely monitored. A total of 8 subjects experienced adverse events of TLS; 3 subjects experienced clinical TLS (that is, 1 event of acute renal failure, 1 case of sudden death associated with TLS, and 1 subject with increased creatinine) and 5 subjects experienced laboratory TLS on the basis of an adverse event being reported. Three additional subjects met laboratory criteria of TLS but had no adverse event reported. Of the 8 subjects with adverse events of TLS, only 1 was enrolled and treated after implementation of Protocol Amendment 8 (post-May 2013), which revised the dose and dosing regimen for the ramp-up period and enhanced TLS prophylaxis/monitoring.

Toxic effects that were reported during ongoing venetoclax therapy in all 116 patients are summarised in Table 39.

Table 39. Adverse Events and Serious Adverse Events in the 116 Study Patients

Adverse eventa	Any Grade N(%)	Grade 3 or 4 N(%)
Any	115 (99)	96 (83)
Diarrhoea	60 (52)	2 (2)
Upper respiratory tract infection	56 (48)	1 (1)
Nausea	55 (47)	2 (2)
Neutropenia	52 (45)	48 (41)
Fatigue	46 (40)	4 (3)
Cough	35 (30)	0
Pyrexia	30 (26)	1 (1)
Anaemia	29 (25)	14 (12)
Headache	28 (24)	1 (1)
Constipation	24 (21)	1 (1)
Thrombocytopenia	24 (21)	14 (12)
Arthralgia	21 (18)	1 (1)
Vomiting	21 (18)	2 (2)
Peripheral oedema	18 (16)	0
Hyperglycemia	17 (15)	10 (9)
Serious adverse event[b]		
Any	52 (45)	
Febrile neutropenia	7 (6)	
Pneumonia	5 (4)	
Upper respiratory tract infection	4 (3)	

Adverse eventa	Any Grade N(%)	Grade 3 or 4 N(%)
Immune thrombocytopenia	3 (3)	
Tumour lysis syndrome	3 (3)	
Diarrhoea	2 (2)	
Fluid overload	2 (2	
Hyperglycemia	2 (2	
Prostate cancer	2 (22 (2	
Pyrexia	(2	

a) Listed are adverse events that were reported in at least 15% of the patients. Preexisting grade 1 or 2 laboratory abnormalities are not reported, unless the grade increased during the study. b) Listed are serious adverse events that were reported in at least two patients. Excluded are serious adverse events that were related to disease progression in two patients.

8.2.2. Study M14-032

Study M14-032 is an open-label, non-randomised, multicenter, Phase II study evaluating the efficacy and safety of venetoclax in subjects with R/R CLL after BCR signalling pathway inhibitor (BCRi) treatment. Total enrolment is planned for 60 subjects. This study has 2 arms, and enrolment is ongoing in both arms:

- Arm A (N = 22 as of data cut-off): subjects with R/R CLL after ibrutinib treatment and
- Arm B (N = 6 as of data cut-off): subjects with R/R CLL after idelalisib treatment.

8.2.2.1. Overall safety summary

All 28 subjects experienced at least 1 treatment-emergent adverse event. The most common treatment-emergent adverse events, regardless of severity or relationship to study drug, were anaemia (10 subjects, 35.7%) and neutropenia, diarrhoea, and nausea (9 subjects, 32.1%, each). Adverse events that were NCI Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 were reported for 22 subjects (78.6%) subjects. The 3 most common Grade 3 or 4 adverse events were anaemia (8 subjects, 28.6%), neutropenia (7 subjects, 25.0%), and thrombocytopenia (5 subjects, 17.9%). Treatment-related adverse events (that is, those adverse events considered with reasonable possibility of being related to study drug), as assessed by the investigator, regardless of severity, occurred in 16 (57.1%) subjects. The most common venetoclax-related adverse events were decreased neutrophil count (7 subjects, 25.0%); neutropenia (4 subjects, 14.3%); anaemia, febrile neutropenia, diarrhoea, increased blood potassium, decreased white blood cell count, and hyperphosphataemia (3 subjects, 10.7%, each).

As of the data cut-off date, 3 subjects had died during the study. All 3 subjects died within 30 days of the last dose of study drug and experienced fatal adverse events (death not otherwise specified, multi-organ failure and malignant neoplasm progression); 2 of these 3 subjects died due to disease progression as determined by the investigator.

Treatment-emergent serious adverse events (SAEs) occurred in 13 subjects (46.4%) as of the data cut-off for this interim report. SAEs of febrile neutropenia, multi-organ failure, pneumonia, and increased blood potassium were reported in 2 subjects (7.1%) each. Treatment-emergent adverse events that led to discontinuation of venetoclax were reported for 4 subjects (14.3%): 2 subjects due to progressive disease (multi-organ failure and malignant neoplasm progression) and 1 subject each because of respiratory failure or death not due to progressive disease. Treatment-emergent adverse events that led to venetoclax dose interruption were reported in

12 subjects (42.9%); events that occurred in ≥ 2 subjects were diarrhoea, increased blood creatinine, increased blood potassium, and hyperphosphataemia (2 subjects each, 7.1%). A treatment-emergent SAE of pneumonia that led to dose reduction was reported for 1 subject (3.6%) after study drug interruption.

Tumour lysis syndrome, neutropenia (including febrile neutropenia) ≥ Grade 3, infections ≥ Grade 3, and second primary malignancy were adverse events of special interest that were closely monitored. One subject had laboratory TLS. Another subject with obstructive lymphadenopathy and renal insufficiency met Howard criteria for laboratory TLS. Neither one of these events were reported as TLS. One subject had two reported events of TLS that did not meet Howard criteria for TLS. One additional subject met laboratory criteria for TLS prior to beginning venetoclax is identified as having pseudohyperkalaemia.

A total of 16 subjects (57.1%) subjects experienced at least one neutropenia-related adverse event (identified using the following preferred terms: neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection, and neutropenic sepsis); 12 subjects (42.9%) reported neutropenia events grade ≥ 3. Neutropenia events that led to venetoclax interruption were reported for 2 subjects (7.1%). A total of 14 subjects (50.0%) subjects experienced at least one adverse event in the Infections and Infestations System Organ Class (SOC); 8 subjects (28.6%) reported grade ≥ 3 infection and infestation events. Infection and infestation events that led to venetoclax interruption were reported for 2 subjects (7.1%). The preferred terms that occurred in ≥ 2 subjects were pneumonia (4 subjects, 14.3%) and lung infection and upper respiratory tract infection (3 subjects, 10.7%, each). The severity and types of infectious events reported were not unusual given this patient population.

8.3. Other supportive combination therapy studies in CLL

Phase Ib Studies M13-365, GO28440, and GP28331

8.3.1. Study M13-365

The primary objectives of this study were to assess the safety profile, determine the maximum tolerated dose (MTD), and establish the Recommended Phase II Dose (RPTD) of venetoclax when administered in combination with rituximab in subjects with relapsed chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL). The tolerability and the optimal lead-in period regimen of the combination were also determined.

The following safety evaluations were performed during the study: adverse event monitoring, vital signs, physical examination, lymphocyte enumeration, 12-lead electrocardiogram (ECG), MUGA/2D echocardiogram, and laboratory assessments. As of the data cut-off for this interim CSR, 49 subjects have been treated with at least 1 dose of venetoclax and are included in the safety population, including 8 subjects in the expanded safety cohort.

8.3.1.1. Overall safety summary

Analysis of overall safety in Study M13-365 at doses from 200 to 600 mg venetoclax led to the selection of 400 mg as the dose to explore further in the safety expansion portion of this study. These included the findings that subjects in Cohort 3 (400 mg) had the numerically lowest rates of Grade 3 or 4 adverse events, Grade 3 or 4 adverse events in the Blood and Lymphatic Disorders SOC, Grade 3 or 4 pooled adverse events for neutropenia, any adverse events in the Blood and Lymphatic Disorders SOC, any adverse events in the Gastrointestinal Disorders SOC, and any adverse events that led to interruption of venetoclax, interruption of rituximab, or reduction of venetoclax. Subjects in the safety expansion cohort (Cohort 6) began enrolment at 400 mg in order to obtain additional safety information at that dose level. When all 16 subjects who received 400 mg of venetoclax (Cohort 3 and Cohort 6, safety expansion) were analysed together, all of the above parameters continued to be numerically lower compared to the other cohorts. In addition, the incidence of adverse events in the General Disorders and

Administration Site Conditions SOC and the Metabolism and Nutrition Disorders SOC were also numerically lower in all subjects who received 400 mg venetoclax. These results contributed to the selection of 400 mg as the RPTD.

- All 49 subjects experienced at least 1 treatment-emergent adverse event. No new risks or an increased severity in identified risks of either venetoclax or rituximab were observed when venetoclax was combined with rituximab.
- Three subjects had fatal adverse events. Two subjects died due to disease progression (Richter's syndrome and malignant neoplasm progression). One subject experienced a fatal event of hyperkalaemia in the setting of TLS on Day 1 after receiving his initial venetoclax dose of 50 mg, prior to implementing lower initial venetoclax doses, a longer lead-in period, and other TLS preventative measures.
- Three subjects experienced treatment-emergent adverse event of TLS (including 1 fatal event) and an additional 2 subjects were identified as having laboratory TLS. Of these 5 total subjects, 2 received an initial venetoclax dose of 50 mg according to the previous dosing regimen. There were no events of TLS following initiation of rituximab combination therapy. Subsequent to implementation of TLS preventative measures, all TLS events were manageable, none fatal or led to discontinuation.
- Events of neutropenia were common with 57.1% of subjects experiencing at least one adverse event of neutropenia. These neutropenic events were reversible following drug interruption, were responsive to growth factor support, and some events were managed while continuing to treat with venetoclax. One subject required rituximab discontinuation, 5 subjects required venetoclax dose reduction, 13 subjects required venetoclax interruption, and 8 subjects required rituximab interruption. Subjects may have had more than 1 change in study drug dosing regimens for neutropenic events.
- A total of 5 subjects experienced grade ≥ 3 infections; none were fatal. The reported infections included respiratory tract infections in 3 subjects and gastrointestinal tract infections in 2 subjects. Three events led to venetoclax interruption and 1 event led to rituximab interruption.
- A total of 8 subjects experienced events potentially related to second primary malignancies, including disease progression in 4 subjects and non-melanoma skin cancers in 4 subjects.

8.3.2. Study GO28440

Title of study: *A Phase Ib, Open-Label Study Evaluating the Safety and Pharmacokinetics of GDC-0199 (ABT-199) in Combination with Bendamustine/Rituximab (BR) in Patients with Relapsed/Refractory or Previously Untreated Chronic Lymphocytic Leukemia.*

8.3.2.1. Primary objectives

The primary objectives were to estimate the maximum tolerated dose and schedule and to evaluate the safety and tolerability of venetoclax (GDC-0199/ABT-199) given in combination with BR to patients with relapsed/refractory (R/R) chronic lymphocytic leukaemia (CLL) and patients with previously untreated CLL.

8.3.2.2. Secondary objectives

The secondary objectives were to characterise the pharmacokinetics (PK) and pharmacodynamics (PD) and to make a preliminary assessment of efficacy of venetoclax in combination with BR when administered to patients with R/R CLL and patients with previously untreated CLL.

8.3.2.3. Study design

Approximately 90 patients were planned to be enrolled. At clinical cut-off, 19 patients were enrolled (12 R/R patients were enrolled under Schedule A: 3 in Cohort 1 (target venetoclax dose 100 mg/day), 3 in Cohort 2 (target venetoclax dose 200 mg/day), and 6 in Cohort 3 (target venetoclax dose 400 mg/day). Two R/R patients were enrolled in Schedule B, (target venetoclax dose 400 mg/day) and five previously untreated patients were enrolled in Schedule A (target venetoclax dose of 400 mg/day).

Bendamustine was administered intravenously (IV) at a starting dose of 70 mg/m^2 for R/R CLL patients or 90 mg/m^2 for previously untreated CLL patients over 30 minutes on 2 consecutive days of each 28-day cycle for 6 cycles. Rituximab was administered IV once per 28-day cycle for up to 6 cycles, in combination with bendamustine. Initial infusion at 375 mg/m^2 (Cycle 1) followed by 500 mg/m^2 (Cycles 2-6).

8.3.2.4. Criteria for safety evaluation

Safety and tolerability were assessed by monitoring vital signs, laboratory tests, electrocardiograms and adverse events (AEs).

8.3.2.5. Overall Safety Summary

All 19 patients received at least one dose of study treatment and were included in the safety evaluable population. Overall, 17 patients (89.5%) experienced at least one treatment-emergent adverse event at the time of the clinical cut-off. There were no deaths or dose limiting toxicities (DLT) reported at the time of the clinical cut-off date.

The most common AEs were neutropenia (9 patients [47.4%]), nausea (8 patients [42.1%]), anaemia (6 patients [31.6%]) and thrombocytopenia (5 patients (26.3%]). The majority of AEs reported (> 74%) were NCI-CTC Grade 1 or 2 in intensity.

Twelve patients (63.2%) experienced NCI-CTC Grade > 3 AEs, the most common being neutropenia (47.4%), thrombocytopenia (15.8%), decreased lymphocyte count, decreased WBC count and leukopenia (each 10.5%). NCI-CTC Grade 3 AEs were reported in 12 patients (63.2%) and NCI-CTC Grade 4 AEs in 5 patients (26.3%). There were no NCI-CTC Grade 5 AEs.

There were a total of 5 SAEs reported in five patients (26.3%). All SAEs were reported in R/R patients in Schedule A, across the cohorts. The SAEs reported were back pain, bronchitis, VIIth nerve paralysis, herpes virus infection and myocardial infarction (MI).

There were no AEs that led to the withdrawal of venetoclax. Adverse events occurred in six patients (31.6%) that led to the withdrawal of bendamustine and/or rituximab, all in R/R Schedule A patients. Adverse events leading to bendamustine and/or rituximab withdrawal were neutropenia, thrombocytopenia, VIIth nerve cell paralysis and decreased white blood cell count.

A total of 49 AEs of special interest were reported occurring in 10 patients (52.6%). Forty-eight of these AEs occurred in 9 R/R patients in Schedule A and one occurred in 1 previously untreated patient in Schedule A. There were no AEs of special interest in Schedule B. The most common adverse event of special interest was Grade ≥ 3 neutropenia, occurring in 9 patients (47.7%). There were no AEs of TLS reported.

No clinically significant changes were observed in vital signs, ECGs or laboratory parameters. Narratives are provided for patients who experienced serious adverse events and for patients who experienced AEs of Grade 3/4 neutropenia or Grade 3/4 infections considered related to venetoclax as assessed by the investigator.

There is insufficient data to make a comparison between the two dosing regimens (i.e. administration of BR before or after the venetoclax dose ramp-up period; Schedule A versus

Schedule B, respectively) with respect to safety, efficacy or PK. The study is ongoing and continues to enrol patients to the dose-finding stage.

8.3.3. Study GP28331

A Phase Ib Multicenter Dose-Finding and Safety Study of GDC-0199 and Obinutuzumab in Patients with Relapsed or Refractory or Previously Untreated Chronic Lymphocytic Leukemia.

8.3.3.1. Primary objectives

- To estimate the maximum tolerated dose (MTD) of venetoclax in combination with obinutuzumab in patients with relapsed/refractory (R/R) chronic lymphocytic leukaemia (CLL) and patients with previously untreated CLL.
- To evaluate the safety and tolerability of venetoclax in combination with obinutuzumab in patients with R/R CLL and patients with previously untreated CLL.

8.3.3.2. Secondary Objectives

- To characterise the pharmacokinetics and pharmacodynamics of venetoclax and obinutuzumab when administered in combination in patients with R/R CLL and patients with previously untreated CLL.
- To make a preliminary assessment of the efficacy of venetoclax in combination with obinutuzumab in patients with R/R CLL and patients with previously untreated CLL, as measured by objective response (OR) rate, response duration, complete response (CR) rate, progression-free survival (PFS), and overall survival (OS).

8.3.3.3. Exploratory Objectives

- To make a preliminary assessment of potential biomarkers that might predict disease response or resistance to treatment with venetoclax in combination with obinutuzumab in patients with R/R CLL and patients with previously untreated CLL.
- To measure minimal residual disease (MRD) at the time of response assessments and its correlation with efficacy parameters.
- To assess the incidence of anti-therapeutic antibodies to obinutuzumab.

8.3.3.4. Study design

Ongoing phase Ib, multicentre, open label, dose-finding and safety study of venetoclax administered in combination with obinutuzumab in patients with CLL. The study is comprised of two stages for each patient population: a dose-finding stage with standard 3 + 3 dose-escalation study design and a safety expansion stage.

Two patient populations are being explored:

- Previously untreated CLL
- R/R CLL.

The dose-finding stage is also exploring two schedules for drug administration, with Schedule A (venetoclax introduced before obinutuzumab) being explored prior to Schedule B (venetoclax introduced after obinutuzumab) for each patient population. The dose-finding stage for each patient population will establish separate MTDs for both Schedule A and Schedule B. Following the dose-finding stage, there will be a single safety expansion stage for each patient population using either Schedule A or Schedule B at its corresponding MTD.

Venetoclax was self-administered orally once daily, starting at 20 mg/day for 1 week, followed by 50 mg/day for 1 week, and continuing sequentially through each cohort each week until the target cohort dose was reached (100, 200, 400 mg/day), then daily dosing until disease progression.

Obinutuzumab was administered by IV infusion at the clinic, with three doses given during Cycle 1 on Days 1, 8, and 15 (the first dose was split over two consecutive days: 100 mg on Day 1 and 900 mg on Day 2), and thereafter on Day 1 of each subsequent cycle for up to six cycles (each cycle is 28 days).

8.3.3.5. Criteria for safety evaluation

Incidence and nature of dose-limiting toxicities (DLTs); adverse events (AEs), serious AEs (SAEs), protocol defined AEs of special interest, laboratory parameters, ECGs and vital signs.

8.3.3.6. Overall Safety Summary

20 patients received at least one dose of either study treatment and were included in the safety evaluable population. Overall, 18/20 patients (90%) experienced at least one treatment-emergent adverse event at the time of the clinical cut-off.

There were no deaths in the study or discontinuations from study treatment due to AEs.

There was one dose-limiting toxicity (laboratory TLS) reported in Cohort 2 (target venetoclax dose 200 mg/day). This event occurred on Cycle 1, Day 3 after the patient resumed venetoclax following the first dose of obinutuzumab. The patient did not develop clinical TLS. No DLTs were observed in the other cohorts. Cohort 3 with a target venetoclax dose of 400 mg/day was selected as the MTD for the R/R patient population treated on Schedule A.

The most common adverse events were diarrhoea (50%); anaemia, neutropenia, and infusion related reaction (each 45%); hyperphosphataemia (40%); nausea and vomiting (each 30%); and fatigue and pyrexia (each 25%). The majority of AEs reported (> 86%) were Grade 1 or 2 in intensity.

Fourteen patients (70%) experienced Grade ≥ 3 AEs, the most common event being neutropenia (40%), tumour lysis syndrome and hyperphosphataemia (each 15%), and neutrophil decreased (10%). All other Grade ≥ 3 AEs were reported in one patient each. There were no Grade 5 AEs.

Serious adverse events were experienced by 7/20 patients (35%). The most common SAE was hyperphosphataemia, which was reported for 2 patients (10%). Other SAEs reported (pneumonia, lower respiratory tract infection viral, cellulitis, device-related infection, lower respiratory tract infection, pyrexia, tumour lysis syndrome, hyperphosphataemia, and neutropenic sepsis) occurred with an incidence of 1 patient. Serious AEs led to dose modifications or interruptions in 4 patients (20%). Overall, three patients (all post-clinical hold) experienced AEs of tumour lysis syndrome in the study. All events were characterised by laboratory abnormalities. The laboratory changes resolved with medical management, and the patients continued in the study. No patients developed any signs or symptoms of clinical TLS.

Preliminary results from this study indicate that the combination of venetoclax at doses up to 400 mg/day with obinutuzumab is well-tolerated in patients with R/R CLL. The safety profile observed in this study is consistent with the safety profiles of the individual agents in CLL.

8.4. Patient exposure

Data from a total of 553 subjects exposed to venetoclax treatment in the pivotal and supportive studies were evaluated for safety. This included exposure to venetoclax treatment at any venetoclax dose administered as monotherapy in CLL (N = 289), combination therapy in CLL (N = 88), monotherapy in NHL (N = 106), and in pharmacology studies (N = 70). Of the 289 subjects with R/R CLL treated with venetoclax monotherapy at any dose, 240 subjects were in the 400 mg dose group.

The safety results from the pivotal monotherapy Study M13-982 in 17p del CLL subjects were largely similar to the safety results in monotherapy Study M12-175 in R/R CLL (Arm A) and in monotherapy Study M14-032 in BCRi failures. Thus, the safety evaluation of 400 mg QD

venetoclax monotherapy was based on the pooled dataset of all subjects who were assigned to 400 mg venetoclax in the 3 monotherapy studies (N = 240) and includes 160 subjects with 17p deletion and 44 subjects who were BCRi failures (not mutually exclusive).

The All 400 mg Analysis Set (N = 240) was treated with venetoclax for an average of 9.1 months (median: 10.3 months) (Table 40), with a maximum exposure of 34.1 months. Approximately 46% (110/240) of subjects received venetoclax for > 48 weeks, including 3 subjects who received treatment for at least 2 years.

Table 40. Exposure to Venetoclax 400 mg QD Monotherapy in R/R CLL

Duration, n (%) of subjects	Alla N = 240	17p Delb N = 160
0 to 5 weeks	9 (3.8)	5 (3.1)
> 5 to 8 weeks	23 (9.6)	14 (8.8)
> 8 to 12 weeks	16 (6.7)	12 (7.5)
> 12 to 16 weeks	12 (5.0)	5 (3.1)
> 16 to 20 weeks	18 (7.5)	11 (6.9)
> 20 to 24 weeks	10 (4.2)	9 (5.6)
> 24 to 28 weeks	7 (2.9)	4 (2.5)
> 28 to 32 weeks	9 (3.8)	7 (4.4)
> 32 to 36 weeks	4 (1.7)	2 (1.3)
> 36 to 48 weeks	22 (9.2)	10 (6.3)
> 48 to 60 weeks	56 (23.3)	46 (28.8)
> 60 to 104 weeks	51 (21.3)	35 (21.9)
> 104 weeks	3 (1.3)	0
Summary Statistics, months		
Mean (SD)	9.1 (6.06)	9.2 (5.42)
Median	10.3	11.1
Min – Max	0.0 – 34.1	0.0 – 21.5

17p del = deletion of the p13 locus on chromosome 17; BCRi = B-cell receptor inhibitor; CLL = chronic lymphocytic leukaemia; R/R = relapsed or refractory; SD = standard deviation

8.5. Adverse events

No clinically important differences were observed between the safety profiles among all subjects in the 400 mg dose groups (N = 240 for all, N = 160 for 17p deletion) or the all doses

groups (N = 289 for all and N = 177 for 17p deletion). The incidence rates in the BCRi Failure Analysis Set (N = 46) were more variable compared with other analysis sets, likely as a result of the smaller sample size. Some AEs, particularly those associated with very aggressive or advanced disease, occurred in a higher percentage of subjects as compared with the other analysis sets.

In the venetoclax All 400 mg Analysis Set, TEAEs were reported in 98.3% of subjects, which included TEAEs coded to the preferred term of malignant neoplasm progression (13 subjects). A medical review confirmed that all cases were related to progression of the primary disease, CLL. When the preferred term of malignant neoplasm progression was excluded, the incidence of TEAEs was 72.9% for Grade 3/4 events, 43.8% for SAEs, 8.8% for TEAEs that led to venetoclax discontinuation, 32.9% for TEAEs that led to venetoclax dose interruption, 9.6% for AEs that led to venetoclax dose reduction, and 4.2% for fatal TEAEs.

When including the preferred term of malignant neoplasm progression, the Grade 3/4 TEAEs in 73.8% of subjects, SAEs in 44.2% of subjects, discontinuations due to TEAEs in 14.2% of subjects, and fatal TEAEs in 7.5% of subjects. The most common TEAE leading to discontinuation was malignant neoplasm progression (13/34), and the majority of fatal TEAEs (11/18) were due to disease progression.

8.5.1. Common Adverse Events

In the All 400 mg Analysis Set, TEAEs of any grade reported in ≥ 10% of subjects were neutropenia (39.2%), diarrhoea (35.4%), nausea (33.3%), anaemia (28.3%), upper respiratory tract infection (21.7%), fatigue (21.3%), thrombocytopenia (18.8%), pyrexia (15.8%), headache (15.0%), vomiting (14.6%), hyperphosphataemia (14.6%), constipation (13.8%), cough (13.3%), hypokalaemia (12.1%), oedema peripheral (10.8%), and back pain (10.0%).

8.6. Laboratory tests

8.6.1. Chemistry

In the All 400 mg Analysis Set (N = 240), the clinical chemistry results for subjects with Grade 0 to 2 baseline values shifted to Grade 3/4 for one or more assessment in ≥ 5% of subjects for low sodium (6.3%), low potassium (8.4%), high potassium (5.1%), low calcium (13.8%), low inorganic phosphate (11.3%), and high glucose (6.4%). At the Final assessment, clinical chemistry variables with shifts to Grade 3/4 for > 2% of subjects were low calcium (2.1%) and high glucose (3.0%).

8.6.2. Liver and Renal Function

No clinically important differences were observed in the incidence of venetoclax AESIs between subjects with normal versus mild and moderate hepatic impairment for the All 400 mg and the All 400 mg 17p Del Analysis Sets.

The incidence of TLS for subjects with moderate renal impairment was 5.9% for All 400 mg and 7.2% for All 400 mg 17p Del; for subjects with normal renal function, the incidence of TLS was 4.4% for All 400 mg and 4.3% for 17p Del.

8.6.3. Electrocardiograms

Electrocardiogram assessments were performed at baseline and at the Final visit in the venetoclax monotherapy Studies M13-982 and M14-032. In Study M12-175, ECG measurements were collected in triplicate at multiple time-matched points at baseline and at steady state. Two subjects with CLL had treatment-emergent abnormal ECG findings that were assessed by the investigator as clinically significant (Study M13-982 CSR and Study M12-175 CSR). The results of ECG findings for both subjects were reported by the investigator as grade 1 TEAEs that were not related to venetoclax (abnormal T waves for Subject [information redacted] in the 400 mg

cohort and sinus tachycardia for Subject [information redacted] in the 600 mg cohort) (Study M13-982 CSR and Study M12-175).

The QTc assessments for venetoclax were performed in monotherapy Study M12-175 and included both subjects with CLL (Arm A) and NHL (Arm B). The ECG measurements were collected in triplicate at multiple time-matched points (2, 4, 6, and 8 h) at baseline (prior to the first dose administration) and at steady state (at 3, 6, or 7 weeks of dose administration) in both Arm A (R/R CLL) and Arm B (NHL). Steady-state doses ranged from 100 to 1200 mg QD. Blood samples for plasma venetoclax assay were collected after each steady-state time matched triplicate ECG collection.

The mean QTcF change from baseline was less than 5 ms at all-time points and dose groups. Furthermore, exposure-response estimates of the mean venetoclax effect on QTc interval across the clinically relevant concentration range were below the threshold level of regulatory concern with the one-sided 95% upper confidence bound < 10 ms at supra-therapeutic doses of 1200 mg, 3-fold higher than the therapeutic dose in CLL subjects (400 mg).

The ECG data and the AE data together indicate that venetoclax is unlikely to have a clinically significant effect on the electrocardiogram QT interval.

8.7. Post-marketing experience

There are no post-marketing data as venetoclax is not marketed in any country.

8.8. Other safety issues

8.8.1. Safety in Special Populations

8.8.1.1. Use in Pregnancy and Lactation

Safety in pregnant women has not been established. There are no adequate and well-controlled studies of venetoclax in pregnant women. Animal data indicate that the risk of teratogenicity is low and there were no other effects on development or fertility. Venetoclax resulted in increased post implantation loss and decreased fetal body weights in the mouse embryofetal development study at 150 mg/kg/day. The background risk of major birth defects and miscarriage for the CLL population is unknown. No placental transfer studies have been conducted to evaluate the potential for exposure of the fetus to venetoclax or assess the presence of venetoclax in breast milk. A total of 2 pregnancies have been reported with venetoclax usage. One pregnancy was reported in the partner of a 55-year-old male who was taking venetoclax in Study GO28667. A live infant with no neonatal complications, congenital anomalies, or birth defects, was delivered. The second pregnancy was reported in systemic lupus erythematosus Study M13 -093 in a subject (20 years of age; 90 mg/placebo cohorts) who had a negative serum beta-hCG on Day 1, but a positive result on Day 28. A live infant with no birth defects was delivered with no medically significant complications. There are no data on the excretion of venetoclax in human milk, the effects of venetoclax on the breastfed child, or the effects of venetoclax on milk production.

8.8.1.2. Drug Interactions

The effects of rifampin and ketoconazole on the pharmacokinetics of venetoclax and the effect of venetoclax on the pharmacokinetics of warfarin are discussed in Section *Summary of results of individual studies*. Coadministration of once daily rifampin, a strong CYP3A4 inducer, decreased venetoclax C_{max} and AUC_{∞} by 42% and 71%, respectively. The Phase I drug-drug interaction study (Study M15-065) between venetoclax and warfarin, a CYP2C9 substrate, was conducted to evaluate the effects of venetoclax on the pharmacokinetics of warfarin Results from this single-dose study in healthy volunteers showed a 18% – 28% increase in C_{max} and AUC_{∞} of R-warfarin and S-warfarin.

8.9. Evaluator's overall comments on safety

The overall clinical safety evaluation of venetoclax for the treatment of CLL included a total of 553 subjects who received at least 1 dose of venetoclax. The venetoclax monotherapy studies in CLL include 1 pivotal study and 2 key supportive ongoing clinical studies. Three ongoing venetoclax combination therapy studies provided supportive safety data. The absence of safety data from randomised controlled trials was noted as a weakness in the application.

Almost all CLL and SLL subjects experienced at least 1 treatment-emergent adverse event. In the monotherapy studies, the most commonly reported related AEs were neutropenia (25% - 41%) and nausea (20%-47%). The 3 most common Grade 3 or 4 adverse events were neutropenia (25%-41%), anaemia (12%-28%), and thrombocytopenia (12%-18%).

Adverse events reported in studies combining venetoclax with rituximab; bendamustine/rituximab; and obinutuzumab were similar to those reported in the monotherapy studies.

Clinical tumour lysis syndrome was observed when venetoclax was initiated in patients with a high tumour burden at doses of 50 mg per day or more. The adoption of a stepwise ramp-up phase, beginning at a daily 20-mg dose with weekly increases to 50 mg, 100 mg, and 200 mg per day to the target dose of 400 mg per day, combined with adherence to prophylaxis and monitoring on the first day of dose increases, reduced the incidence of laboratory evidence of the tumor lysis syndrome with no clinical tumor lysis syndrome. Current Phase II and III trials of venetoclax in patients with CLL have been designed to confirm that this risk can be mitigated with the use of TLS protocols.

Based on the safety data provided by the Sponsor, venetoclax monotherapy and combination therapy for the treatment of R/R CLL, has demonstrated a favourable safety profile as demonstrated by the frequency and severity of AEs, SAEs, AEs leading to discontinuation, and select AEs. The consistency of the venetoclax safety results across trials underlines the reliability of the risk assessment provided by the sponsor. The safety profile of venetoclax combination therapy was similar to that of venetoclax alone.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of venetoclax in the proposed usage are:

- In patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion, the overall response rate with venetoclax monotherapy is 79.4%.
- In patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion, the complete response rate with venetoclax monotherapy is 7.5%.

9.2. First round assessment of risks

The risks of venetoclax in the proposed usage are:

- Tumour lysis syndrome
- Neutropenia

With the current venetoclax dosing schedule and prophylaxis, the risk of tumour lysis syndrome has been reduced and is manageable.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of Venclexta for the treatment of patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion is favourable.

There are insufficient data provided with regard to the clinical efficacy of Venclexta monotherapy or combination therapy with rituximab, bendamustine/ obinutuzumab in relapsed/refractory chronic lymphocytic leukaemia patients to provide an assessment of benefit-risk. However, the safety profile of Venclexta combination therapy is similar to that of Venclexta alone.

10. First round recommendation regarding authorisation

Based on the clinical data, submitted it is recommended that the application, '*Venclexta (venetoclax) is indicated for the treatment of patients with chronic lymphocytic leukaemia who have received at least one prior therapy; this includes patients with 17p deletion'*, not be approved.

In the pre-submission meeting, it was noted that the TGA had commented on the proposed Indication being broad compared to the data set, in which the main study only included 17 p del patients and that the Indication statement defined the target population in terms of receipt of prior treatment rather than relapsed or refractory, which did not fully reflect the patient population.

Based on the clinical data submitted, it is recommended that the sponsor change the indication to: '*Venclexta is indicated for the treatment of patients with relapsed or refractory chronic lymphocytic leukaemia with 17p de*letion.'

11. Clinical questions

1. It was considered that inadequate evidence was provided for the validity of ORR as a surrogate endpoint for efficacy and effect duration in R/R CLL. Please provide a more detailed justification for the use of ORR as the primary measure of efficacy, rather than PFS or OS.
2. It is currently considered that the standard retreatment for R/R CLL patients who have relapsed greater than 3 years after initial treatment, is FCR4 and that high-risk groups such as those with early failure (< 3 years), who are not suitable for FCR retreatment, would benefit most from newer novel agents. It was noted that the Inclusion criteria for subjects in studies presented by the sponsor was for refractory or relapsed CLL subjects. Please justify the Indication for 'patients who have received one prior therapy' rather than 'relapsed or refractory CLL.'

12. Second round evaluation of clinical data submitted in response to questions

12.1. Question 1

It was considered that inadequate evidence was provided for the validity of ORR as a surrogate endpoint for efficacy and effect duration in R/R CLL. Please provide a more detailed justification for the use of ORR as the primary measure of efficacy, rather than PFS or OS.

12.1.1. Sponsor response

Approval of a drug application is based on endpoints that demonstrate that a drug provides longer life, a better life, or a favourable effect on an established surrogate for a longer life or a better life. In the United States, modification of the new drug application in 1992 allowed for the accelerated approval of drugs for diseases that are serious or life-threatening when the new drug appears to provide benefit over available therapy, but under situations when the demonstrated benefit did not yet meet the standard for regular approval. Between 1990 and 2002, the United States Food and Drug Administration (FDA) approved 71 marketing applications for oncology drugs. Of these, 57 were granted regular approval and 14 were granted accelerated approval.[2] Endpoints other than survival were the basis for approval for 75% of these applications (39 of 57 regular approvals and 14 of 14 accelerated approvals). In particular, tumour response alone was the basis of approval in 54% of applications (26 of 57 regular approvals and 12 of 14 accelerated approvals).

The FDA Guidance for Industry on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, states that tumour response, or objective response rate (ORR), should be defined as the sum of complete responses (CR) and partial responses (PR).

When defined in this manner, ORR is a direct measure of a drug's anti-tumour activity, and thus can be evaluated in a single arm study.[3] The Guidance adds that tumour endpoint assessments generally should be verified by central reviewers blinded to study treatments. The use of ORR is common due to the belief that ORR is likely to predict clinical benefit in patients with serious or life-threatening diseases, which is applicable to most types of refractory cancers. In certain refractory tumours, ORR is accepted as a valid measure of anti-tumour activity in single-arm Phase II studies because objective responses are never seen in the absence of treatment.

In the EMA Guideline on the evaluation of anticancer medicinal products in man (December 2012), when ORR is used to evaluate single agent anti-tumour activity, it should follow international standards with modifications in certain situations with justification, the intent to treat principle should be adhered to, and external independent review of tumour response is encouraged.[4] Data on duration of response, progression free survival and overall survival should also be reported. All of these guidelines have been adhered to for this submission.

Fludarabine was approved in 1991 as a regular approval for patients with chronic lymphocytic leukaemia (CLL) refractory to at least one prior standard alkylating agent containing regimen.[5] Fludarabine was studied in two single-arm open-label studies comprised of 48 and 31 patients. Approval was based on ORR of 48% and 32% respectively, with a CR rate of 13% in both studies, and a median duration of disease control of 21 and 15 months. The approval was also based on improvement in anaemia and thrombocytopenia.

Ofatumumab was approved in 2009 for the treatment of patients with CLL refractory to fludarabine and alemtuzumab. The label noted that the effectiveness of ofatumumab was based on the demonstration of durable objective responses and that no data demonstrated an improvement in disease related symptoms or increased survival. The approval was based on a single-arm multi-centre study in 154 patients. The investigator determined ORR was 42% with a median duration of response of 6.5 months. There were no complete responses.

Other agents for haematological malignancies that have received regular approval based on tumour response alone include arsenic trioxide, cladribine, pentostatin, teniposide and

[2]Johnson JR, Williams G, Pazdur R. End points and United States Food and Drug Administration approval of oncology drugs. J Clin Oncol. 2003;21(7):1404-11.
[3]FDA. Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. May 2007.
[4]EMA. Guideline on the evaluation of anticancer medicinal products in man. European Medicines Agency. EMA/CHMP/205/95/Rev.4. 13 December 2012
[5]FLUDARA (fludarabine) [package insert] Cambridge, MA; Genzyme Corporation, 2010. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020038s033lbl.pdf.

tretinoin. For these refractory haematological indications, the surrogate endpoint was complete response of adequate duration. A second review of FDA approvals from 2002 to 2012 showed similar results. Over 66% of regular approvals and over 75% of accelerated approvals were based on endpoints other than overall survival. Regular approval of oncology drugs based on tumour response alone indicates that this endpoint is considered a surrogate for better life and the possibility of improved survival in certain clinical settings.

Patients who have relapsed CLL with 17p deletion have extremely poor prognosis. Patients treated with fludarabine, cyclophosphamide and rituximab do extremely poorly and have only 5 month median PFS. Other studies have revealed similar low response rates in relapsed/refractory patients with 17p deletion CLL (Table 41).

Table 41. Historical data on R/R CLL with 17p deletion

Drug/Regimen	CLL Population	Number of 17p Deleted Patients Enrolled	ORR	PFS
Ofatumumab[8]	double refractory	31	29%	PFS 5.7 m
Alemtuzumab#[9]	relapsed/refractory	31	39%	PFS 5.8 m
Alemtuzumab#+ steroids[10]	relapsed*	22	77%	PFS 6.5 m
Bendamustine + Rituximab[11]	relapsed/refractory	14	7%	PFS 6.8 m
FCR[7]	relapsed	20	35%	PFS 5 m

* In 17p deleted patients only.

\# The marketing authorisation for Alemtuzumab has been withdrawn at the request of the marketing-authorisation holder.

Study M13-982 demonstrates that treatment with venetoclax is associated with dramatic anti-cancer activity in a difficult to treat population, due to restoration of apoptosis in CLL cells via Bcl-2 inhibition. In terms of clinical response, the ORR was 74.8% (CR = 19.6%) in the main efficacy cohort of the study, as assessed by investigators and this high response rate was further validated by an independent review committee (ORR = 79.4%; CR = 7.5%). The secondary endpoints of the study provide further evidence that response to venetoclax translates to improved outcome. In particular, duration of response (DOR) was sustained with a median DOR of 27.5 months and a median PFS of 24.7, both consistent with durable clinical benefit. To date, the 24-month overall survival observed in the study was 70% while the median overall survival had not been reached. The large magnitude of improvement seen with venetoclax for all endpoints suggest that the robust anti-tumour effect demonstrated in terms of ORR are predictive of prolonged clinical benefit in these high-risk patients.

In summary, ORR is a valid endpoint with which to evaluate the clinical benefit of venetoclax. This conclusion is substantiated by the following: (1) a strong mechanistic rationale based on the dependence of CLL cells on Bcl-2 for survival, (2) demonstration of high rates of response in very high-risk patient populations with poor prognoses and high unmet need, (3) durability of these responses, and (4) consistency between ORR and important secondary endpoints, such as PFS and OS, that are indicative of long-term improvements in clinical outcome.

12.1.2. Evaluation of response

It was recognised that durable ORR for venetoclax for the treatment of relapsed/refractory CLL has provided sufficient evidence for accelerated approval by the US FDA on the condition that the sponsor conducts clinical studies to verify and describe the actual benefit. Furthermore, if the post-marketing studies fail to demonstrate clinical benefit, venetoclax may be removed from the market. It was also recognised that the Sponsor has defined ORR by the sum of CR, Cri, nPR and PR, and that as defined, ORR is a direct measure of venetoclax activity for the treatment of CLL. In determining whether the use of ORR as a surrogate endpoint which is likely to predict

clinical benefit, the significance of ORR and availability of alternative therapies have been taken into consideration as follows:

The significance of ORR was assessed by its magnitude and duration and the percentage of complete responses in relapsed/refractory CLL patients with very poor prognosis treated with currently approved targeted and chemotherapeutic agents. In the pivotal study M13-982, CR was achieved in 8% and 17% in the IRC and Investigator assessments respectively. Nodular PR and PR were achieved in 81% and 62% in the IRC and Investigator assessments respectively. Although the majority of responses were partial, the overall response in this population of relapsed/refractory CLL subjects with 17p deletion was durable. As of the data cut-off of the interim CSR, per IRC assessment, DOR had been evaluated in 85 subjects in the main cohort who had a record of first response (CR, CRi, PR or nPR). The Kaplan-Meier estimate of the proportion of subjects with a durable response at 12 months was 84.7% per IRC assessment and the Kaplan-Meier estimate of the proportion of subjects with PFS at 12 months was 72.0%.

Considering the poor historical outcome data in this population of patients, with ORR between 7 and 77% and PFS 5 to 6.8 months, it was considered that the sponsor had provided evidence of significant ORR. Furthermore, the sponsor has provided evidence of durability of response, which is expected to provide symptomatic benefit with respect to decreased blood product transfusion requirements, infection and constitutional well-being. It was therefore determined that ORR was sufficient evidence of clinical efficacy for use of venetoclax in relapsed/refractory CLL; whilst waiting for mature PFS and/or OS data, the following statements should be added to the PI:

- at the beginning of the Clinical Trials section of the PI:
- *'The approval for the use of Venclexta® in CLL is based on Phase I and Phase II non-randomised trials. The results of a randomised, active-controlled Phase III study are awaited.'*
- the Indications section of the PI:
- '*Note to Indication. The indication is approved based on overall response rates. Duration of response and improvements in overall survival, progression-free survival or health-related quality of life have not been established.'*
- This 'Note to the indication' must be included in all marketing documentation for venetoclax.

12.2. Question 2

It is currently considered that the standard retreatment for R/R CLL patients who have relapsed greater than 3 years after initial treatment, is FCR and that high-risk groups such as those with early failure (< 3 years), who are not suitable for FCR retreatment, would benefit most from newer novel agents. It was noted that the Inclusion criteria for subjects in studies presented by the sponsor was for refractory or relapsed CLL subjects. Please justify the Indication for 'patients who have received one prior therapy' rather than 'relapsed or refractory CLL.'

12.2.1. Sponsor response

The sponsor acknowledges the evaluator's comment, and has revised the indication within the PI to reflect 'relapsed or refractory CLL' as opposed to 'patients who have received one prior therapy.'

12.2.2. Evaluation of response

The sponsor has revised the indication within the PI to reflect 'relapsed or refractory CLL' as opposed to 'patients who have received one prior therapy'.

12.3. Comment 1

Based on the clinical data, submitted it is recommended that the application, 'Venclexta (venetoclax) is indicated for the treatment of patients with chronic lymphocytic leukaemia who have received at least one prior therapy; this includes patients with 17p deletion', not be approved.

In the pre-submission meeting, it was noted that the TGA had commented on the proposed Indication being broad compared to the data set, in which the main study only included 17 p deletion patients, and that the Indication statement defined the target population in terms of receipt of prior treatment rather than relapsed or refractory, which did not fully reflect the patient population.

Based on the clinical data submitted, it is recommended that the sponsor change the indication to: 'Venclexta is indicated for the treatment of patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion.'

12.3.1. Sponsor response

The sponsor acknowledges the TGA's recommendation regarding the broader relapsed/refractory (R/R) chronic lymphocytic leukaemia (CLL) population group and has restricted the indication to the 17p deletion R/R population as follows:

Venclexta is indicated for the treatment of relapsed or refractory chronic lymphocytic leukaemia (CLL) with 17p deletion.

However, the sponsor would like to propose an addition to the Indication statement taking into account comments made on the R/R CLL population within the Clinical Evaluation Report. The sponsor believes that there remains an unmet medical need in a subset of R/R CLL patients for whom there are no other available treatment options. Venetoclax has the ability to meet this need, and thus, the following revised indication statement is proposed:

> *Venclexta is also indicated for the treatment of patients with relapsed or refractory CLL without the 17p deletion for whom there are no available treatment options.*

12.3.1.1. Unmet Medical Need in R/R CLL Patients

A substantial unmet medical need remains for treatments that improve response, maintain remission, provide a more favourable safety profile and achieve long-term control of CLL in patients with and without the 17p deletion.

For the treatment of relapsed and refractory disease, current European Society for Medical Oncology (ESMO) guidelines[6] recommend a change in therapeutic regimen to one of the following: Bcl-2 antagonists alone or in combination within a clinical study; Bruton's tyrosine kinase (BTK) inhibitor ibrutinib; PI3K inhibitor idelalisib in combination with rituximab; or other chemoimmunotherapy combination only if TP53 mutation is not present. Patients not responding to therapy with kinase inhibitors may be switched to a different kinase inhibitor or to a Bcl-2 antagonist in the context of a clinical trial. Current British Committee for Standards in Haematology interim guidelines[7] are similar to the ESMO guidelines and recommend ibrutinib or idelalisib plus rituximab; patients with relapsed CLL who do not meet the criteria for idelisib or ibrutinib should be treated with chemotherapy with or without rituximab.

Unfortunately, currently available treatments used to treat patients with R/R CLL have, for the most part, been either associated with significant toxicities, such as increased risk of serious infections including opportunistic infections and significant bone marrow suppression, or provided limited disease control (low response rates and limited progression free survival

[6] Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Annal Oncol. 2015;26 (Suppl 5):vi78-84

[7] Follows GA, Bloor A, Dearden C, et al. Interim statement from the BCSH CLL Guidelines Panel. 2015. Available from: http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html.

[PFS]), or both. Subsequently, these unfavourable treatment outcomes have led to a population of R/R CLL patients with no other available treatment options. Despite the efficacy shown for the fludarabine, cyclophosphamide, and rituximab (FCR) regimen in R/R CLL, it is not indicated for over half of all CLL patients due to intrinsic toxicity of the regimen and comorbidities common in the CLL population.[8] For patients experiencing disease progression after treatment with aggressive chemoimmunotherapy, outcomes tend to be poor, particularly for those patients who fail early (for example, fludarabine-based combination therapy within the first 2 to 3 years).[9] The combination regimen of bendamustine and rituximab (BR) has an improved toxicity profile relative to FCR and is active in patients progressing after fludarabine-based treatment but disease control with this regimen is disappointingly short in R/R CLL patients with median PFS of 11.1 to 15.2 months in recent trials.[10] However, neither bendamustine alone nor bendamustine-containing regimens are indicated for treatment of CLL relapsed or refractory to second line chemo-immunotherapy and therefore do not represent a readily available treatment option to many patients in Australia. Ofatumumab is indicated in Australia as monotherapy for R/R CLL patients who are refractory to fludarabine and alemtuzumab. Although toxicity is modest, clinical response is also modest with objective response rates (ORR) of 42% with no complete responses and duration of response of 6.5 months. Obinutuzumab in combination with chlorambucil is indicated only in the frontline setting for patients with coexisting conditions. In this setting, median PFS was 26.7 months with this combination.

Patients failing or who are deemed unsuitable for treatment with a B-cell receptor inhibitor (BCRi; for example, ibrutinib or idelalisib) are an emerging subpopulation with R/R CLL, and those who progress early on ibrutinib are being identified as very high unmet medical need due to having poor outcomes.[11] Additional reports support these initial findings on patients failing BCRi inhibitors. In a single institution report by Sandoval-Sus et al, the median overall survival (OS) for subjects with disease progression after ibrutinib was 5.5 months. In another report from a single institution, 33 of 127 subjects had discontinued ibrutinib.[12] Of those who discontinued, 21% were due to CLL progression, 21% due to disease transformation and 33% due to adverse events. The adverse events included events of bleeding, colitis, diarrhoea, infection, and ulceration. Median OS in this population was 3.1 months. Barrientos et al[13] reported similarly poor prognoses for R/R CLL subjects discontinuing idelalisib with a median OS of approximately 2 months. Finally, response rates of CLL subjects on BCRi therapy after discontinuing another BCRi therapy were also low. The ORR for subjects on idelalisib-based therapy following ibrutinib discontinuation was 50% (n = 12; 42% partial response [PR], 8% partial response with lymphocytosis [PR-L]). Subjects on ibrutinib-based therapy following idelalisib discontinuation fared better with an ORR of 77% (n = 13; 54% PR, 23% PR-L).14 At

[8]Stilgenbauer S, Furman RR, Zent CS. Management of chronic lymphocytic leukemia. Am Soc Clin Oncol Educ Book. 2015:164-75.

[9]Brown JR. The treatment of relapsed refractory chronic lymphocytic leukemia. Hematology. 2011;2011(1):110-8.

[10] Fischer K, Cramer P, Busch R, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 2011;29(26):3559-66.

Chanan-Khan A, Cramer P, Demirkan F, et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. Lancet. 2016;17(2):200-11.

Zelenetz AD, Robak T, Coiffier B, et al. Idelalisib plus bendamustine and rituximab (BR) is superior to BR alone in patients with relapsed/refractory chronic lymphocytic leukemia: results of a phase 3 randomized double-blind placebo-controlled study. Blood. 2015;126(23). Available from: http://www.bloodjournal.org/content/126/23/LBA-5.

[11]Böttcher S, Hallek M, Ritgen M, et al. The role of minimal residual disease measurements in the therapy for CLL: is it ready for prime time? Hematol Oncol Clin North Am. 2013;27(2):267-88.

[12]Jain P, Keating M, Wierda W, et al. Outcomes of patients with chronic lymphocytic leukaemia (CLL) after discontinuing ibrutinib. Blood. 2015;125(13):2062-7.

[13]Barrientos JC, Kaur M, Mark A, et al. Outcomes of patients with lymphocytic leukemia (CLL) after idelalisib therapy discontinuation. Blood. 2015;126(23). Available from: http://www.bloodjournal.org/content/126/23/4155.

present, the reports from these single institutions, with patients who may or may not have been on clinical trials, are the only means of comparison. Therefore, patients have limited options if they are unable to tolerate or are unsuitable for treatment with a BCRi.

In light of overall toxicities related to FCR and idelalisib, and limited efficacy in subsets of patients who cannot tolerate or who are unsuitable for treatment with second line treatments such as chemo-immunotherapy and/or BCR inhibitors, a clear unmet need continues to exist for which venetoclax represents a viable option for the treatment of R/R CLL, in patients with or without 17p deletion (as discussed below).

12.3.1.2. Venetoclax Mechanism of Action

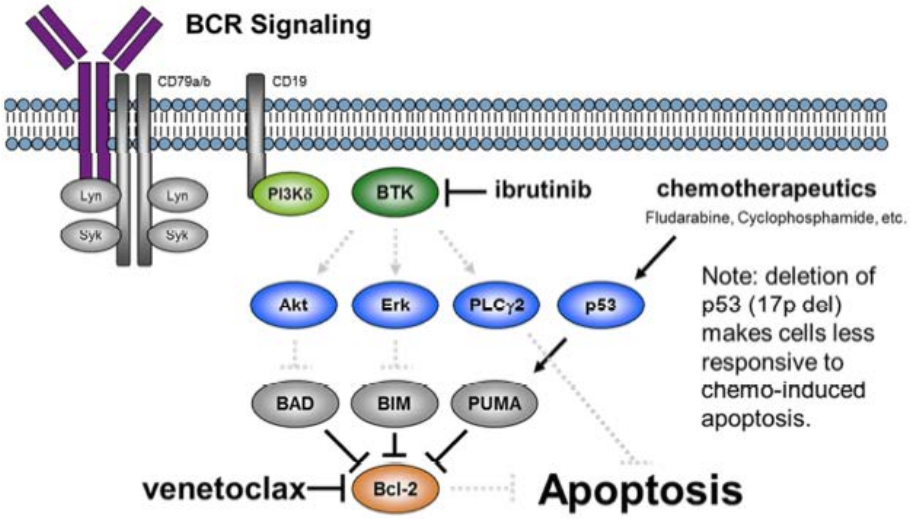
Venetoclax fulfils the unmet need by providing an effective therapy to patients with R/R CLL disease and also provides advantages over other available therapies based on a unique mechanism of action.

Many chemotherapeutics used in treating CLL, including fludarabine, cyclophosphamide, and bendamustine, act by inducing deoxyribonucleic acid (DNA) damage and triggering apoptosis. The p53 tumor suppressor is essential for relaying the DNA damage signal to the apoptotic machinery via up-regulation of BH3-only proteins like NOXA and PUMA.[14] When p53 is functionally inactivated, either through mutation or deletion, these signals are not relayed effectively, blunting the efficacy of these agents.[15]

However, venetoclax with its unique mechanism of action bypasses these signalling events and inhibits Bcl-2 directly (Figure 19), and therefore, is expected to be equally effective irrespective of 17p deletion and TP53 mutation status in the tumors. When primary CLL patient samples were cultured with venetoclax ex vivo, the 17p deletion samples were, on average, just as sensitive to venetoclax as the non-17p deletion samples, with cell killing EC50 values in the low 10 – 20 nM range.

Figure 19: Venetoclax mechanism of action bypass p53 and other signalling pathways

[14] Zhu HJ, Fan L, Zhang LN, et al. The BH3-only protein Puma plays an essential role in p53-mediated apoptosis of chronic lymphocytic leukemia cells. Leuk Lymphoma. 2013;54(12):2712-9.
Mackus WJ, Kater AP, Grummels A, et al. Chronic lymphocytic leukemia cells display p53-dependent drug-induced puma upregulation. Leukemia. 2005;19(3):427-34.
[15]Badoux XC, Keating M, O'Brien S, et al. Patients with relapsed CLL and 17p deletion by FISH have very poor survival outcomes. Blood. 2009;114. [Abstract 1248].
Stilgenbauer S, Zenz T, Winkler D, et al. Subcutaneous alemtuzumab in fludarabine-refractory chronic lymphocytic leukemia: clinical results and prognostic marker analyses form the CLL2H study of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 2009;27(24):3994-4001



Bcl-2 = B-cell lymphoma-2; BCR = B-cell receptor; BTK = Bruton's tyrosine kinase

Targeted agents designed to inhibit chronically active B-cell receptor (BCR) signalling (for example, the BTK inhibitor ibrutinib and the PI3Kδ inhibitor idelalisib) also act in part by inducing apoptosis. Apoptosis triggered by these agents also requires a series of signalling events that are subject to mutation. For example, resistance to ibrutinib can arise through mutations in BTK itself (C481S) or downstream signalling effectors such as PLCγ2 (R665W). Again, because it targets Bcl-2 directly, venetoclax should maintain efficacy against CLL cells bearing these mutations as well.

Population pharmacokinetic/pharmacodynamic exposure response analysis included a dataset of subjects with baseline somatic mutations (17p deletion, 11q deletion, 12q trisomy, and 13q deletion). It was determined that these baseline mutations were not a significant covariate affecting venetoclax exposure response. Based on this analysis, the clinical evaluator concluded equal sensitivity between patients who did and did not harbour the 17p deletion mutation. Specifically that '*subjects with the 17p deletion chromosomal aberration appeared to be as sensitive to the effects of venetoclax as subjects who did not have the 17p deletion'* (Clinical Evaluation Report). This conclusion is consistent with that drawn by the evaluator of the Orphan Drug Designation (ODD) request, submitted on 05 December 2014. In this request, The sponsor applied for orphan drug status specifically in CLL patients harbouring the 17p deletion mutation, who are regarded as having the poorest prognosis within the CLL population. The ODD application was rejected by the TGA on the 31 July 2015, on the grounds that there was no 'biologically plausible reason' why the product would not be as efficacious in the broader R/R CLL group. Venetoclax is Efficacious in R/R CLL Patients, With or Without the 17p Deletion In light of the opinion provided in the Clinical Evaluation Report regarding insufficient data provided in the original submission for TGA to assess the benefit/risk in R/R CLL patients, The sponsor believes it is important to provide selected longer-term follow-up data, particularly in comparing 17p deletion vs non-17p deletion patients, from the key study, Study M12-175. Therefore, updated efficacy data from the original submission to the TGA (10 February 2015 data cut) to a 10 June 2016 data cut for Study M12-175 are provided below. Safety data are not provided because there are no clinically significant changes compared to the data provided in the original submission; however, the data are available on request.

In Study M12-175, 67 subjects with R/R CLL or SLL who had received venetoclax at 400 mg were available for analysis. As of 10 June 2016, median time on study was 24.7 (range: 0.5 – 50.1) months. Of these 67 subjects, 57 subjects had assessments by both independent review committee (IRC) and investigator; data from the 57 subjects are presented in the tables below. Of the 57 subjects, 5 subjects either did not have assessment of 17p deletion status or the status

was indeterminate, 12 subjects had 17p deletion and 40 subjects did not have 17p deletion. Investigator assessed ORR was similar for those with or without 17p deletion (75.0% or 80.0%, respectively) (Table 42).

The median PFS was 15.6 months for those with 17p deletion and 41.4 months for those without 17p deletion (Table 43). These data demonstrate that response is obtained in all R/R CLL patients. The response is durable in patients with 17p deletion and even more durable in patients without 17p deletion.

Table 42. Investigator assessed response Study M12-175

	n (%) [95% CI]			
Subject Response[a]	Updated Results 17p del Subjects N = 12[b]	Updated Results No 17p del Subjects N = 40[b]	Updated Results All Subjects[c] N = 57	Previous Results All Subjects[d] N = 57
ORR	9 (75.0) [42.8, 94.5]	32 (80.0) [64.4, 90.9]	46 (80.7) [68.1, 90.0]	46 (80.7) [68.1, 90.0]
CR rate (CR + CRi)	0	6 + 0 (15.0) [5.7, 29.8]	7 + 1 (14.0) [6.3, 25.8]	5 + 2 (12.3) [5.1, 23.7]
nPR rate	0	2 (5.0)	2 (3.5)	2 (3.5)
PR rate	9 (75.0)	24 (60.0)	36 (63.2)	37 (64.9)
Stable disease	3 (25.0)	6 (15.0)	9 (15.8)	9 (15.8)
Disease progression	0	1 (2.5)	1 (1.8)	1 (1.8)
Incomplete data	0	1 (2.5)	1 (1.8)	1 (1.8)

CI = confidence interval (95% CI is from the exact binomial distribution); CR = complete remission; CRi = complete remission with incomplete marrow recovery; nPR = nodular partial remission; PR = partial remission

a. Data are investigator assessed response for the N = 57 subjects who also had IRC assessed response.
b. Of the 57 subjects, 12 subjects had 17p deletion and 40 subjects did not have 17p deletion;17p deletion status was indeterminate or not assessed for 5 subjects.
c. Data cut-off for updated results: 10 June 2016.
d. Data cut-off for previously reported results: 10 Februaruy 2015.

Table 43. Investigator assessed duration of response and PFS in Study M12-175

Endpoint[a]	Updated Results 17p del Subjects N = 12[b]	Updated Results No 17p del Subjects N = 40[b]	Updated Results – All Subjects[c] N = 57	Previous Results – All Subjects[d] N = 57
DOR,[e] n	9	32	46	46
Median	14.4 [12.1, --]	40.3 [40.1, --]	40.1 [24.0, --]	NR [14.1, --]
12 months	100.0 [100.0, 100.0]	93.1 [75.1, 98.2]	95.1 [81.9, 98.8]	96.6 [77.9, 99.5]
24 months	29.2 [4.2, 61.9]	76.3 [53.1, 89.0]	68.4 [48.9, 81.8]	NA
PFS				
Median[f]	15.6 [2.0, --]	41.4 [17.2, --]	41.4 [17.2, --]	NR [15.6, --]
12 months[g]	75.0 [40.8, 91.2]	79.2 [62.6, 89.0]	80.2 [67.1, 88.5]	79.3 [65.4, 88.0]
24 months	32.8 [8.2, 60.9]	65.3 [47.8, 78.2]	62.0 [47.4, 73.7]	NA

DOR = duration of response; NR = not reached; NA = not available; OS = overall survival; PFS = progression-free survival

a. Data are investigator assessed for the N = 57 subjects with IRC assessments.
b. Of the 57 subjects, 12 subjects had 17p deletion and 40 subjects did not have 17p deletion; 17p deletion status was indeterminate or not assessed for 5 subjects.
c. Data cut-off for updated results: 10 June 2016.
d. Data cut-off for previously reported results: 10 February 2015.
e. n = subjects with objective response; data are % [95% CI].
f. Data are months [95% CI].
g. Data are % [95% CI].

As discussed above, patients who relapse or are refractory to the currently available therapies have very limited treatment options. As shown in Table 44, venetoclax is effective in R/R CLL patients with ≥ 3 prior therapies; ORR in these subjects ranged from 60.9% to 90.0% for Study M12-175. Collectively, these updated efficacy data support the use of venetoclax in R/R CLL patients for whom there are no available treatment options.

Table 44. Activity of venetoclax in R/R CLL subjects by prior number of therapies

	Study M12-175		
Investigator Assessed Response[a]	**3 Prior Therapies N = 7**	**4 Prior Therapies N = 10**	**≥ 5 Prior Therapies N = 23**
ORR (95% CI)	85.7 (42.1, 99.6)	90.0 (55.5, 99.7)	60.9 (38.5, 80.3)
CR rate (CR + CRi)	0	20.0 (2 + 0)	4.3 (1 + 0)
Median PFS (months)	NR	15.7 (7.4, 41.5)	27.3 (3.8, 41.4)

CR = complete remission; NR = not reached; ORR = objective response rate; PFS = progression-free survival

a. Subjects dosed with 400 mg in Study M12-175. Data cut-off is 10 June 2016.

In summary, the current, unmet need in R/R CLL is for treatments that improve response, maintain remission, and achieve long-term control of CLL with optimal quality of life. Venetoclax has proven as an efficacious treatment for CLL population with the unique ability to achieve deep responses including complete remission and minimal residual disease (MRD) status (pivotal Study M13-982, included with the original submission) and efficacy in the broader R/R CLL population, including patients with or without the 17p deletion (Study M12-175, updated data). In addition, a sub-population of R/R CLL patients has exhausted currently available treatments either due to lack of response, intolerability or unsuitability of currently available CLL therapies. With the unique mechanism of action and favourable tolerability profile, venetoclax offers an alternative therapy with for these patients who have no other therapeutic options.

12.3.2. Evaluation of response

The sponsor's response to restrict the indication to Venclexta is indicated for the treatment of relapsed or refractory chronic lymphocytic leukaemia (CLL) with 17p deletion' is satisfactory.

The proposal to include 'Venclexta is also indicated for the treatment of patients with relapsed or refractory CLL without the 17p deletion for whom there are no available treatment options' has been considered as follows:

The sponsor provided results from 3 studies, M12-175, M13-365, and M14-032, which included CLL subjects negative for the 17p deletion. Study M12-175, was a dose escalation and safety expansion Phase I study in subjects with R/R CLL/SLL; M13-365 was a Phase Ib, open-label, multicentre study evaluating the safety and tolerability of venetoclax in combination with rituximab in subjects with relapsed CLL or SLL; and M14-032 evaluated the efficacy and safety of venetoclax monotherapy in subjects with CLL relapsed after or refractory to treatment with B-cell receptor signalling pathway inhibitors. All efficacy analyses for M12-175 and M13-365 were exploratory and preliminary results were presented for M14-032.

The sponsor has provided updated data on M12-175. As of June 2016, median time on study was 24.7 (range: 0.5 – 50.1) months. Of 67 subjects, 57 subjects had assessments by both IRC and investigator. Of the 57 subjects, 5 subjects either did not have assessment of 17p deletion status or the status was indeterminate, 12 subjects had 17p deletion and 40 subjects did not have 17p deletion. Investigator assessed ORR was similar for those with or without 17p deletion (75.0% or 80.0%, respectively). The median PFS was 15.6 months for those with 17p deletion and 41.4 months for those without 17p deletion. Considering these data, it was recognised that responses were obtained in R/R CLL patients with and without 17p deletion. Furthermore, the response was durable in patients with and without 17p deletion.

For Study M13-365, 19.6% (9 of 46) had 17p deletion. Tumour response was evaluated by the investigator in all 49 subjects across all dose cohorts. The ORR was 81.6%, the CR rate was 36.7% and the deep response rate (CR + CRi + nPR) was 40.8%. The estimated proportion of subjects with a durable response at 12 months was 93.1% and the median duration of response had not been reached. The Kaplan-Meier estimate for subjects without progression at 12 months was 88.7% and the median time to progression had not been reached. Subgroup analysis was performed for subjects with 17p deletion (n = 9) and showed that the ORR was 66.7%.

For Study M14-302, 32.1% (9 of 28) of subjects had 17p deletion, and 28.6% (8 of 28) had a TP53 mutation, all of whom also had 17p deletion. Of the 22 subjects who had previously failed ibrutinib therapy, 15 had completed the first response assessment at 8 weeks, with results of PR (53.3%), SD (40.0%) and not evaluable (6.7%) due to baseline disease burden in the bone marrow only. Of these 15 subjects, one, who had a confirmed PR at Week 24, developed progression due to Richter's transformation at Week 29. All others remain on study. Of the 6 subjects who had previously failed idelalisib, 4 had completed the first response assessment at 8 weeks, with results of PR (50.0%), SD (25.0%) and PD (25.0%). In total, 10 of 19 (52.6%) evaluable subjects had a response of PR.

Population pharmacokinetic/pharmacodynamic exposure response analysis included a dataset of subjects with baseline somatic mutations (17p deletion, 11q deletion, 12q trisomy, and 13q deletion). It was determined that these baseline mutations were not a significant covariate affecting venetoclax exposure response.

In conclusion, subjects without the 17p deletion chromosomal aberration appeared to be as sensitive to the effects of venetoclax as subjects who had the 17p deletion and it is recommended that the following revised indication statement be included:

> *'Venclexta is also indicated for the treatment of patients with relapsed or refractory CLL without the 17p deletion for whom there are no available treatment options.'*

This additional indication must also be marketed with the same note to the indication described above:

> *'Note to Indication. This indication is approved based on overall response rates. Duration of response and improvements in overall survival, progression-free survival or health-related quality of life have not been established.'*

12.4. Comment 2

A favourable risk-benefit balance for venetoclax monotherapy and combination therapy has been demonstrated for R/R CLL subjects with 17p deletion, and early data are favourable for R/R CLL across all molecular prognostic groups; however, the results of more mature data are awaited and a Phase III study which will compare the efficacy of venetoclax plus rituximab with bendamustine plus rituximab is ongoing. Therefore, the following statement should be added to the beginning of the clinical trials section of the PI:

> *The approval for the use of Venclexta® in CLL is based upon Phase II non-randomised trials. The results of a randomised, active-controlled Phase III study are awaited.*

In the studies provided, ORR has been used as a surrogate end-point for PFS. Whilst waiting for mature PFS and/or OS data, the following statement should be added to the Indication in the PI:

> *Note to Indication. The indication is approved based on overall response rates. Duration of response and improvements in overall survival or health-related quality of life have not been established.*

Small numbers of subjects have been studied in non-randomised trials, and consequently the true adverse event rate cannot yet be described. A box warning at the beginning of the PI and CMI should be used to highlight the following specific serious adverse events, which need to be brought to the attention of the prescriber and patient:

WARNING

The following have occurred in patients receiving Venclexta®:

§ *Tumour lysis syndrome, which may be life-threatening or fatal*

§ *Haematological toxicities, which may be severe or life-threatening*

Interrupt or discontinue Venclexta® as recommended if these adverse events occur (See Precautions and Dosage and Administration).

12.4.1. Sponsor response

The sponsor acknowledges the evaluator's recommendations, and has made the following revisions to the PI:

· The following statement has been added to the beginning of the Clinical Trials section of the PI, with a slight modification to reflect Study M12-175 as a Phase I clinical trial:

· *'The approval for the use of Venclexta® in CLL is based on Phase I and Phase II non-randomised trials. The results of a randomised, active-controlled Phase III study are awaited.'*

· The following statement has been added to the Indications section of the PI:

'Note to Indication. The indication is approved based on overall response rates. Duration of response and improvements in overall survival or health-related quality of life have not been established.'

The sponsor believes that the routine risk minimisation activities outlined in the RMP and ASA (that is, the strength of wording within the PI and CMI, the design of the monthly starting pack and associated language to facilitate adherence to the dose escalation schedule and the quick start guide), in addition to supporting activities (see below) that the sponsor intends to implement once Venclexta is commercialised, are sufficient in negating any safety concerns related to TLS that would warrant the need for a black box warning.

Proposed Supporting Activities

· HCP Venclexta Onboarding = Education, initiation checklist assessment and support tools.

· Patient On-Boarding = Monthly starter kit, patient education materials, patient alert card, appointment schedule and opt-in support program for reminders.

· Additional AbbVie online support portal & AbbVie medical information phone support.

· Limited access program = During this time AbbVie intends to monitor and assess all HCP education and patient on-boarding programs to ensure applicability and safety prior to broader availability.

The sponsor has made revisions to the 'Tumour Lysis Syndrome' section of the PI to highlight TLS as a serious adverse event (potentially life-threatening/fatal) and to interrupt/discontinue therapy if TLS occurs. The text is bolded and positioned at the beginning of 'Precautions' to highlight this to the prescriber. Prophylactic measures with respect to TLS, as detailed in the 'Dosage and Administration' section, has also been revised and presented in a tabular format consistent with the measures followed in the protocols in order to provide physicians with clear and prescriptive information and avoid any risk of error.

Additionally, the Australian Specific Annex (ASA) to the RMP, for which an updated version has been provided with this response (Version 1.1), contains routine risk minimisation activities

specifically for TLS, which includes the PI and Quick Start Guide (in the form of a package insert to be included with the Monthly Starter Pack). The Guide provides clear instruction to the patient regarding hydration, scheduling of blood tests, and the need to contact their healthcare support team on Day 2 of each week before continuing with treatment during the dose-escalation phase. AbbVie submits that the revisions made to the PI, in addition to routine risk minimisation activities as detailed in the ASA and the proposed supporting activities outlined in this response are sufficient in negating any safety concerns in relation to TLS that would warrant the need for a boxed warning.

Neutropenia is a common toxicity in patients with R/R CLL who have received multiple prior chemotherapy/immunotherapies, reported in 40% to 60% of patients.1-3 With the exception of 2 subjects with 17p deletion who were treatment naïve, all subjects had received at least one prior treatment regimen (median: 3; range: 1 – 12). Of the 240 subjects in the All 400 mg Analysis Set, 27.5% had low neutrophil counts at baseline, 16.3% of subjects had used G-CSF within the 6 months prior to initiating venetoclax treatment, and 20.4% had a medical history of neutropenia.

Neutropenia AESIs were reported in 46.7% (112/240) of subjects, and the reported preferred terms were neutropenia, neutrophil count decreased, and febrile neutropenia as shown in Table 45.

Table 45. Neutropenia AESIs: Venetoclax monotherapy in R/R CLL (monotherapy analysis sets)

	Number (%) of Subjects				
	Venetoclax 400 mg QD		Venetoclax All Dose		
TEAE (MedDRA v17.1)	All[a] N = 240	17p Del[b] N = 160	All[a] N = 289	17p Del[b] N = 177	BCRi Failure[c] N = 46
All Neutropenia AESIs[d]	112 (46.7)	71 (44.4)	136 (47.1)	81 (45.8)	24 (52.2)
by Preferred Term					
Neutropenia	94 (39.2)	63 (39.4)	118 (40.8)	73 (41.2)	14 (30.4)
Neutrophil count decreased	20 (8.3)	6 (3.8)	20 (6.9)	6 (3.4)	9 (19.6)
Febrile neutropenia	13 (5.4)	9 (5.6)	18 (6.2)	11 (6.2)	6 (13.0)
NCI CTCAE grade ≥ 3 AESI	101 (42.1)	65 (40.6)	123 (42.6)	74 (41.8)	20 (43.5)
Serious AESI	14 (5.8)	10 (6.3)	19 (6.6)	12 (6.8)	4 (8.7)
AESI led to					
Discontinuation of venetoclax	0	0	0	0	0
Interruption of venetoclax	14 (5.8)	9 (5.6)	20 (6.9)	11 (6.2)	4 (8.7)
Reduced dose of venetoclax	10 (4.2)	8 (5.0)	17 (5.9)	11 (6.2)	0
Death	0	0	0	0	0

17p del = deletion of the p13 locus on chromosome 17; AESI = adverse event of special interest; BCRi = B-cell receptor inhibitor; CLL = chronic lymphocytic leukemia; CTCAE = Common Terminology Criteria for Adverse Events (version 4); NCI = National Cancer Institute; R/R = relapsed or refractory; TEAE = treatment-emergent adverse event

a. Subjects with R/R CLL in Studies M13-982, M12-175 Arm A, and M14-032.
b. Subjects with R/R CLL harboring 17p del; Studies M13-982, M12-175 Arm A, and M14-032.
c. Subjects with R/R CLL who previously failed BCRi therapy; Studies M13-982, M12-175, and M14-032.
s. Includes preferred terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection, and neutropenic sepsis.

The risk of neutropenia decreased over time. The large majority of neutropenia AESIs (97/112) first occurred within the first 60 days of venetoclax treatment. The first onset of neutropenia AESIs was greatest (42.5% of subjects, which represents 102 of the 112 subjects with events) during the first 90 days of venetoclax treatment and decreased to 6.3% during the next 90 days and to less than 3% for each 90-day interval thereafter. Neutropenia, especially higher grades,

can predispose a patient to risk of infection. For patients receiving venetoclax, there was no apparent correlation between neutropenia and infection rates.

The majority of subjects who developed Grade ≥ 3 neutropenia AESIs did not have associated infections.

Of the 101 subjects who experienced Grade ≥ 3 neutropenia AESIs any time during the study, only 12 (11.9%) experienced serious infection AESIs within 7 days before or after the neutropenia AESI.

Furthermore, review of the SAEs of neutropenia did not identify any apparent correlation with concurrent infection in the majority of the cases.

There were no apparent differences in the types of infections observed in subjects who were neutropenic versus those who were not neutropenic at the time of infection.

There were no dose discontinuations due to neutropenia and the percentage of dose interruptions or reductions were 6.2% or lower.

Thus, neutropenia and the more relevant issue of infections associated with neutropenia do not merit black box warning status.

The sponsor has included additional minor revisions to the PI for the evaluator's consideration. These changes are highlighted with appropriate justification in the annotated copy of the revised PI provided for ease of reference.

The sponsor provides an assurance that these additional changes do not impact on the scope and scale of the submission, and serve to ensure that the draft content is accurate, concise, and grammatically appropriate. Specifically, the incidence of TLS as detailed under 'Adverse effects,' has been updated from 12 to 13% as Subject 165 in Study M12-175 had an AE of TLS (laboratory TLS) added since the original filing of the dossier

12.4.2. Evaluation of response

It was considered that the sponsor's risk minimisation activities contained in the risk management plan and Australian Specific Annex (ASA) to the RMP, in addition to the planned supporting activities related to tumour lysis syndrome were adequate to reverse the recommendation for a black box warning.

It was considered that the sponsor's responses to concerns around haematological toxicities were adequate and reversed the recommendation for a black box warning.

12.5. Comment 3

Given the early nature of the efficacy data presented, and lack of directly comparable safety data, a credit card-sized patient card listing key adverse events should be developed and provided to patients for use in emergency.

As per Section 11.2, a box warning at the beginning of the CMI should be used to highlight the following specific serious adverse events, which need to be brought to the attention of the prescriber and patient:

'WARNING

The following have occurred in patients receiving Venclexta:

- *Tumour lysis syndrome, which may be life-threatening or fatal. Moderate renal dysfunction (creatinine clearance [CrCl] < 80 mL/min) increases the risk of tumour lysis syndrome.*
- *Haematological toxicities, which may be severe or life-threatening Interrupt or discontinue Venclexta® as recommended if these adverse events occur (See Precautions and Dosage and Administration).'*

12.5.1. Sponsor response

The sponsor agrees to develop a patient alert card, which will list the key adverse events for emergency use. The sponsor proposes to provide this patient alert card directly to the patient as part of the on-boarding process at the initiation stage.

The sponsor also provided a response in relation to the evaluator's request for a box warning for the PI and CMI.

The sponsor has revised the CMI and added a warning statement under 'What is in this leaflet' which highlights that TLS can be fatal, and instructs the patient to ensure they adhere to healthcare professional instructions, appointments and blood tests. It also provides instruction that patients with kidney problems (or have a history of kidney problems) may have increased risk of TLS, and should advise their healthcare professional accordingly.

Annotated and clean copies of the revised CMI are provided for the Evaluator's consideration.

12.5.2. Evaluation of response

The sponsor has agreed to develop a patient alert card which will list the key adverse events for emergency use and will provide the alert card directly to the patient as part of the on-boarding process at the initiation stage.

The sponsor has adequately revised the CMI.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

The benefits of venetoclax in the proposed usage are:

- In patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion, the overall response rate with venetoclax monotherapy is 79.4%.
- In patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion, the complete response rate with venetoclax monotherapy is 7.5%.
- In patients with relapsed or refractory chronic lymphocytic leukaemia, those without the 17p deletion chromosomal aberration appear to be as sensitive to the effects of venetoclax as subjects who have the 17p deletion.

13.2. Second round assessment of risks

The risks of venetoclax in the proposed usage are:

- Tumour lysis syndrome
- Neutropenia

With the current venetoclax dosing schedule and prophylaxis, the risk of tumour lysis syndrome has been reduced and is manageable.

Both proposed indications are based upon the early analysis of non-randomised trials and as such the comparative difference in incidence of adverse events cannot be categorically described until the results from randomised clinical trials are reported. Given the small number of venetoclax-exposed patients without 17p deletion (n< 100), the incidence of adverse events which are uncommon, rare or very rare cannot be satisfactorily reported currently.

13.3. Second round assessment of benefit-risk balance

- The benefit-risk balance of Venclexta for the treatment of patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion is favourable.
- The benefit-risk balance of Venclexta for the treatment of patients with relapsed or refractory chronic lymphocytic leukaemia without 17p deletion, and for whom there are no available treatment options, is favourable, noting the paucity of safety data currently available from the limited number of patients treated.

14. Second round recommendation regarding authorisation

Based on the clinical data submitted, approval is recommended for the following application:

> *Venclexta is indicated for the treatment of:*
>
> - *Patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) with 17p deletion, or*
> - *Patients with relapsed or refractory CLL for whom there are no other suitable treatment options.*
>
> *Note to Indications. These indications are approved based on overall response rates. Duration of response and improvements in overall survival, progression-free survival or health-related quality of life, have not been established.*

(Note the pluralisation of the 'Note to the indication')

15. References

1. Badoux, X. C., et al. (2011). 'Cyclophosphamide, fludarabine, alemtuzumab, and rituximab as salvage therapy for heavily pretreated patients with chronic lymphocytic leukemia.' Blood 118(8): 2085-2093.
2. Badoux, X. C., et al. (2011). 'Fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy is highly effective treatment for relapsed patients with CLL.' Blood 117(11): 3016-3024.
3. Tam, C. S., et al. (2008). 'Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia.' Blood 112(4): 975-980.
4. Tam, C. S., et al. (2014). 'Long-term results of first salvage treatment in CLL patients treated initially with FCR (fludarabine, cyclophosphamide, rituximab).' Blood 124(20): 3059-3064.

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