13 October 2016
EMA/725631/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Venclyxto

International non-proprietary name: venetoclax

Procedure No. EMEA/H/C/004106/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

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
BCRi	B Cell receptor inhibitor
BMI	body mass index
BR	bendamustine rituximab
CD	cluster of differentiation
CI	confidence interval
CLL	chronic lymphocytic leukaemia
CPP	Critical process parameter
CQA	Critical Quality Attribute
CR	complete remission
CRi	complete remission with incomplete bone marrow recovery
CSR	clinical study report
CT	computed tomography
CTLS	clinical tumour lysis syndrome
CYP	cytochrome P
DNA	deoxyribonucleic acid
DOR	duration of overall response
DSC	Differential Scanning Calorimetry
ECCr	estimated creatinine clearance rate using Cockcroft Gault formula
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
Ecrf	electronic case report form
EFS	event free survival
EORTC	European Organization for Research and Treatment of Cancer
EQ VAS	European Quality of Life -Visual Analogue Scale
EQ-5D-5L	European Quality of Life 5 Dimensions 5 Levels Questionnaire
ESMO	European Society for Medical Oncology
FCR	fludarabine cyclophosphamide and rituximab
FISH	fluorescence in situ hybridization
FT-IR	Fourrier Transform Infrared Spectroscopy

G CSF	granulocyte colony stimulating factor
GC	Gas Chromatography
GC-MS	Gas chromatography mass spectrometry
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
IC	Ion chromatography
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgA, IgG, IgM	immunoglobulin A, immunoglobulin G, immunoglobulin M
IgVH	immunoglobulin variable region heavy chain
IHC	immunohistochemistry
IPC	In-process control
IR	Infrared
IRB	Institutional Review Board
IRC	Independent Review Committee
ITP	idiopathic thrombocytopenic purpura
IU	International Units
IUO RUO	investigational use only research use only
IUPAC	International Union of Pure and Applied Chemistry
IV	intravenous
IWCLL	International Workshop for Chronic Lymphocytic Leukaemia
LDH	lactate dehydrogenase
LDPE	Low Density Polyethylene
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
MS	Mass Spectrometry
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI WG	National Cancer Institute Working Group
NHL	non Hodgkin s lymphoma
NMR	Nuclear Magnetic Resonance
Npr	nodular partial remission
NPT	non protocol anti lymphoma therapy
ORR	overall response rate
OS	overall survival
PBT	Persistent, bioaccumulative, toxic

PCR	polymerase chain reaction
PD	pharmacodynamics
PDE	Permitted Daily Exposure
PE	Polyethylene
PET	positron emission tomography
PFS	progression free survival
PG	pharmacogenetics
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
PLM	Polarised light microscopy
PP	Polypropylene
PR	partial remission
PT	prothrombin time
PVC	Poly vinyl chloride
QbD	Quality by design
QC	Quality Control
QLQ C30	Quality of Life Questionnaire Core 30
QLQ CLL16	Quality of Life Questionnaire Chronic Lymphocytic Leukaemia 16
QoL	quality of life
QWP	Quality Working Party
RH	Relative Humidity
RNA	ribonucleic acid
RPTD	the recommended Phase 2 dose
RRT	Relative retention time
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SLL	small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
SMQ	standardized MedDRA query
SOC	system organ class
STP	sewage treatment plant
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment emergent adverse event
TGA	Thermo-Gravimetric Analysis
TLS	tumour lysis syndrome
TSE	Transmissible Spongiform Encephalopathy
TTNT	time to next anti CLL treatment
TTP	time to progression
ULN	upper limit of normal
USP	United States Pharmacopoeia
UV	Ultraviolet
vPvB	very persistent and very bioaccumulative
WBC	white blood cell
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AbbVie Ltd. submitted on 13 November 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Venclyxto (venetoclax), through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 October 2014.

Venetoclax was designated as an orphan medicinal product EU/3/12/1080 on 06 December 2012. Venetoclax was designated as an orphan medicinal product in the following indication: treatment of chronic lymphocytic leukaemia.

The applicant applied for the following indication:

Venetoclax is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) in the presence of 17p deletion or TP53 mutations.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of venetoclax as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The applicant indicated that venetoclax was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's request(s) for consideration

Conditional Marketing Authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14(7) of the above mentioned Regulation based on the following claims:

a) Medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases;

b) Medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) No 141/2000.

New active Substance status

The applicant requested the active substance venetoclax, contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 17 January 2013, 23 January 2014, 06 February 2014 and 22 January 2015. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries: United States.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Pieter de Graeff

- The application was received by the EMA on 13 November 2015.
- The procedure started on 4 December 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 22 February 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 22 February 2016.
- PRAC assessment overview, adopted by PRAC on 17 March 2016 .
- During the meeting on 1 April 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 1 April 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 May 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 29 June 2016.
- During the CHMP meeting on 21 July 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 August 2016.

- During the CHMP meeting on 13 September 2016, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 13 October 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Venclyxto.
- The CHMP adopted a report on similarity of Venclyxto with Arzerra, Gazyvaro and Imbruvica on 13 October 2016

2. Scientific discussion

2.1. Introduction

Chronic lymphocytic leukaemia (CLL) is a progressive haematologic disease characterized by an accumulation of monoclonal mature B cells in the blood, bone marrow, and secondary lymph organs, and diagnosis requires the presence of ≥5000 B-lymphocytes/µL in the peripheral blood for the duration of at least 3 months. It is the most common form of adult leukaemia in the Western world, representing about 30% of leukaemias, with higher incidences in North America and Europe than in Asia, with an incidence of 4 per 100,000 persons per year. In Europe, the age-standardised CLL incidence rate from the United Kingdom Clinical Practice Research Datalink was 6.2/100,000 person years. The median age of diagnosis in the EU is 72 years and only 10% of patients are less than 55 years old. The current WHO classification system recognizes and groups CLL and small lymphocytic lymphoma (SLL) as the same biological entity, with CLL clinically manifesting primarily in bone marrow and peripheral blood, and SLL primarily manifesting in the lymph nodes.

Current treatments for CLL are not curative. Fewer patients obtain responses with each subsequent regimen, and subjects become increasingly resistant to available therapy. Patients who relapse after a disease-free period of over 1 year (2-3 years for chemoimmunotherapy) are considered treatment sensitive and may be candidates for treatment reinitiation. Patients who relapse after a shorter interval, or are refractory to first-line treatment, present a more challenging group, particularly those who are older, have comorbid conditions, and/or harbor high-risk cytogenic abnormalities. A retrospective analysis of patients in the German CLL8 trial found that overall survival after the start of salvage treatment among patients whose disease had progressed within 2 years after the end of chemoimmunotherapy was about 2 years, comparable to that of truly refractory patients. In the EUROCARE-5 registry, the survival rate for patients with CLL at 5 years post diagnosis was 69.0%.

Patients with a genetic mutation with 17p del or a mutation of the tumour suppressor gene TP53 have a poor prognosis, with a median overall survival (OS) of 2 to 5 years. Approximately 5% to 10% of patients with early stage CLL have a 17p del and/or TP53 mutation; this rate increases with treatment lines up to 40% in advanced refractory CLL. Approximately 80% of CLL patients with a 17p del also have a mutation in TP53; sole TP53 mutations in the absence of 17p del have been reported to occur in approximately 4% to 5% of patients.

The monoclonal antibody ofatumumab, is currently approved in the EU in the treatment of CLL in the relapsed or refractory setting as a single agent. The combination of the monoclonal antibody rituximab with chemotherapy (eg, fludarabine and cyclophosphamide) (FCR regimen) is approved in the EU for use in this setting. Marketing authorization for alemtuzumab, which had been indicated for the treatment of CLL in patients for whom fludarabine combination chemotherapy is not appropriate, was withdrawn in the EU in August 2012.

Allogeneic haematopoietic stem cell transplantation (HSCT) is the only treatment option with the potential to cure CLL; however most patients are not fit for HSCT and the benefits must be weighed against the risks for each patient. Historically, the prognosis for 17p del CLL patients has been poor due to the limited efficacy of immunotherapy and chemoimmunotherapy-based regimens. A median progression free survival (PFS) of 14 months has been reported in first-line 17p deletion patients and 6 to 7 months in relapsed/refractory (R/R) 17p del patients; median OS was approximately 24 months.

Recent introduction of targeted therapy, such as BCR inhibitors (BCRi), has improved the treatment options for CLL patients with the 17p del or TP53 mutation. Ibrutinib was associated with independent review committee (IRC) assessed objective remission rate (ORR) of 48% to 65% (investigator assessed ORR of 83% to 86%) and idelalisib/rituximab was associated with IRC assessed ORR of 85%. In 2014, Imbruvica (ibrutinib) and Zydelig (idelalisib) in combination with rituximab were approved for treatment of CLL patients that have received at least one prior therapy and first-line treatment in the presence of 17p del or TP53 mutation in patients unsuitable for chemo-immunotherapy.

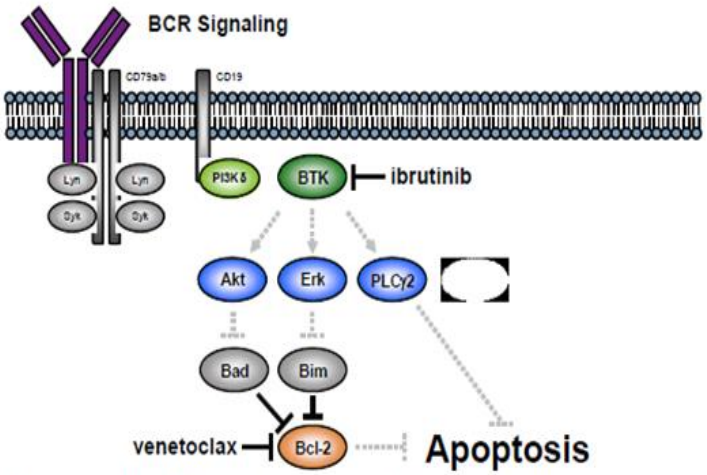
The recently updated European Society for Medical Oncology (ESMO) guidance reflects these approvals and recommends that patients with 17p del or TP53 mutation are treated with B-cell receptor inhibitors (BCRi), i.e. ibrutinib; idelalisib + rituximab) in front-line and R/R settings.

Venclyxto (INN: Venetoclax also referred to as ABT-199 and GDC-0199) is a novel, orally bioavailable, small-molecule B-cell lymphoma (Bcl)-2 family inhibitor in the biarylacylsulfonamide chemical class. Anti-apoptotic Bcl-2 family members are associated with tumour initiation, disease progression, and chemotherapy resistance. Overexpression of Bcl-2 is a major contributor to the pathogenesis of some lymphoid malignancies; antagonism of the action of these proteins may enhance response to therapy and overcome resistance, and thus, these proteins are compelling targets for anti-tumour therapy.

Aberrant expression of Bcl-2 is common in CLL and CLL cells typically have a fundamental reliance on Bcl-2 for survival. Moreover, in CLL and other tumour types or subpopulations, Bcl-2 is highly associated with or pre-bound to pro-death proteins such as Bim (Bcl-2 interacting mediator of cell death), a status described as "primed for death." In this state, the cells may be driven into apoptosis by treatment with a Bcl-2 inhibitor.

Venetoclax acts downstream in the B-cell receptor signaling cascade, and is also expected to maintain activity in the presence of identified mutations (see figure below).

Figure 1: Mechanism of Action of Venetoclax and ibrutinib in Inhibition of BCR Pathway Signalling



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

The applicant is seeking the indication: "Venclyxto is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) in the presence of 17p deletion or TP53 mutations, or who are unsuitable for or have failed a B-cell receptor pathway inhibitor". Following the assessment, the indication was revised as:

- Venclyxto monotherapy is indicated for the treatment of chronic lymphocytic leukaemia (CLL) in the presence of 17p deletion or *TP53* mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor.
- Venclyxto monotherapy is indicated for the treatment of CLL in the absence of 17p deletion or *TP53* mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.

Venclyxto is orally administered presented as film coated tablets proposed as a starting dose of 20 mg once daily for 7 days, to be gradually increased over a period of 5 weeks up to the recommended daily dose of 400 mg.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film coated tablets containing 10 mg, 50 mg or 100 mg of venetoclax as active substance.

Other ingredients are:

Tablet core: copovidone K value 28, colloidal anhydrous silica (E551), polysorbate 80 (E433), sodium stearyl fumarate, anhydrous calcium hydrogen phosphate (E342 (ii)).

Film-coating: polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 3350 (E1521), talc (E553b), iron oxide yellow (E172). Additionally, for 50 mg strength, iron oxide red (E172) and iron oxide black (E172).

The product is available in PVC/PE/PCTFE aluminium foil blisters as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of venetoclax is 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-({3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzamide corresponding to the molecular formula $C_{45}H_{50}ClN_7O_7S$. It has a relative molecular mass of 868.44 g/mol and the following structure (Figure 2):

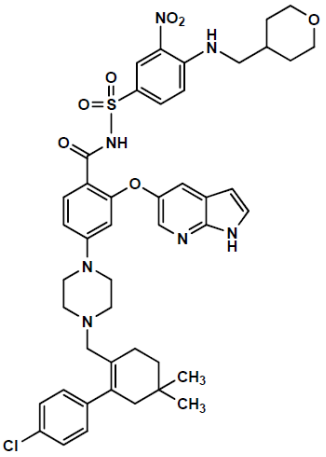


Figure 2: Structure of venetoclax

Venetoclax is a light yellow to yellow to dark yellow non-hygroscopic powder with a melting point of about 138 ºC onset. Its solubility in aqueous media is very low and it is very slightly soluble in 1% polysorbate 80 (w/v aq.). The apparent permeability is in the low to moderate range. The pK_a values are 3.4 and 10.3 for the sulfonamide and piperazine groups respectively and the partition coefficient is 5.5. Venetoclax has a non-chiral molecular structure.

Polymorphism has been observed for venetoclax. Multiple crystal forms have been discovered in solid form screening studies. The thermodynamically stable form is consistently manufactured and does not change upon storage.

The Applicant has performed comparative structural analysis to show that venetoclax is to be regarded as a new active substance (NAS) in itself and that it is not a salt, complex, derivative or isomer (nor mixture of isomers) of a previously authorised substance. Venetoclax has not been previously authorised in any medicinal product in the EU.

Manufacture, characterisation and process controls

Venetoclax is synthesized in four main stages, using four well defined starting materials with acceptable specifications. Each manufacturing stage is divided into unit operations and each unit

operation may have one or more process steps to produce the crystalline form selected for manufacture. Several manufacturing sites are involved in the manufacture of the active substance. Where common intermediates are manufactured by different sites, identical synthetic route and materials (catalyst, reagents and solvents) are used.

A process step or a sequence of process steps may be repeated and it is confirmed that the reprocessed material must meet the specification. The proposed reprocessing is considered acceptable.

A systematic approach to manufacturing process development and control strategy has been taken and the following key elements were addressed throughout development: identification of the potential venetoclax critical quality attributes that are linked to the finished product quality target product profile; identification through prior knowledge, experimentation and risk assessment of the material attributes, process parameters, and critical unit operations that can impact the venetoclax active substance CQAs; use of process understanding in combination with quality risk management to establish the active substance control strategy.

The manufacturing process has been developed using a combination of conventional univariate studies and elements of QbD such as risk assessment, design of experiment (DoE) studies and kinetic modelling, but no design space has been claimed. Critical and non-critical process parameters have been described. A thorough understanding of the formation and fate of impurities in venetoclax process was obtained by a combination of spiking and purging studies and process stress studies. The obtained knowledge was used to establish impurity acceptance criteria for the starting materials and isolated intermediates, which in combination with in process controls and the established processing ranges ensure the quality of venetoclax active substance. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents are considered acceptable. A detailed control strategy, which identifies the primary control points (i.e. starting material and API intermediate controls, in-process controls, and process parameters) throughout the manufacturing, has been established and justified. The control strategy is considered satisfactory.

Detailed information on the development of the commercial manufacturing process has been provided. Venetoclax is currently manufactured by the four-stage process. The proposed commercial process has been used for stability and validation batches and most clinical studies. Earlier processes have been used in non-clinical, first-in-human studies, and early clinical batches. The differences of these earlier processes compared to the commercial process have been described. Changes introduced have been presented in sufficient detail and have been justified.

Process validation has been completed and shows that the manufacturing process can perform effectively and reproducibly to obtain venetoclax meeting its predetermined specifications and quality attributes.

The Venetoclax crystalline form selected for manufacture has been characterised by MS, FT-IR, ^{1}H NMR, ^{13}C NMR, XRPD, DSC, TGA, laser diffraction for particle size distribution, optical microscopy, dynamic vapour sorption (DVS) and UV/VIS. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed, with regards to their origin, and characterised. The potential presence of genotoxic and carcinogenic impurities has been satisfactorily addressed and where relevant adequate limits for these impurities have been included in the control strategy.

The active substance is packaged in bags placed in light protective drums used for storage/shipping of the active substance. The primary packaging complies with Ph. Eur. requirements and EC 10/2011 as amended.

Specification

The active substance specification, includes tests for: description (visual), solution clarity and colour (Ph. Eur.), identification (IR, HPLC), crystal form (XRPD), assay (HPLC), impurities (HPLC), residual solvents (GC, GC MS), sulphated ash (Ph. Eur.), water content (Ph. Eur.), microbiological quality (Ph. Eur.). The active substance specifications are based on the active substance critical quality attributes (CQA).

Impurities present at higher level than the qualification threshold according to ICH Q3A were qualified by toxicological studies and appropriate specifications have been set.

The omission in the specification of certain tests has been adequately justified. Solvents used in the process prior to stage 4 and certain reagents have been shown to be acceptably cleared in venetoclax. The catalyst has not been detected in batch analysis data and, at a daily dose of 400 mg, does not exceed the permissible daily exposure considered acceptable by ICH Q3D. Therefore, it is considered justified that these parameters are not included in the specification.

The genotoxic or potentially genotoxic impurities, including genotoxic impurity precursors and carcinogenic impurities that could be formed or introduced during the venetoclax manufacturing process are controlled through material attributes and/or by controls in compliance with the options defined in the ICH M7.

Moreover, a number of active substance quality attributes considered as non-critical are not included in the specification and it is considered acceptable.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines. The stability indicating nature of the methods for assay and impurities was demonstrated by means of forced degradation studies. Satisfactory information regarding the reference standard used for assay and impurities testing has been presented.

Batch analysis data are provided for twenty eight venetoclax batches manufactured by the commercial process at production scale and above. Eight of the batches were manufactured at the commercial manufacturing site. Most of the batches have been used for clinical purposes. In addition, batch results from batches manufactured by earlier processes have been provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data were provided for five production scale or greater than production scale batches of active substance in the intended commercial package for up to 12 months under long term conditions at 30 ºC / 75% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH. Photostability testing following the ICH guideline Q1B was performed on one primary batch. Stability results at refrigerated conditions (5 ºC) and at elevated temperatures (50 ºC / 75% RH and 60 ºC / 75% RH) were also provided for the three primary batches. In addition, process validation batches manufactured at the proposed manufacturing site have been placed on stability but results are not available yet.

Although the formal stability studies have not been performed according to the storage conditions proposed by ICH Q1A (R2), as higher humidity of 75% is used instead of 65%, this is acceptable as no decomposition is observed due to humidity.

The following parameters were tested: description, assay, water content, impurities and crystal form (XRPD). At some storage conditions microbiological quality and water activity are also monitored. Some changes were made to the analytical methods during stability studies. The changes to the

analytical test methods did not affect the interpretation of the stability results. Changes have been described and the validation summaries for the old methods have been provided.

No significant change in any of the parameters tested has been observed during the formal stability studies and no trends are seen. All tested parameters were within the specifications. No difference in trends is seen between the results of the primary stability batches and the stability batches manufactured at the proposed commercial site.

Venetoclax exhibits sensitivity to light. Changes were not seen in the long term and accelerated stability studies where venetoclax was packaged in plastic bags and placed in the stability chamber. The substance in the plastic bags will however be stored in outer plastic drums to ensure protection from light.

From stress studies it was found that venetoclax is sensitive to oxidation and slightly sensitive to UV radiation, heat, heat and moisture and acid treatment. Although stress studies under basic conditions were not performed, early physicochemical properties studies on venetoclax demonstrated that the active substance is stable under alkaline conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months at the proposed storage conditions of NMT 30 ºC in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product comes in three strengths of venetoclax (10 mg, 50 mg and 100 mg) as immediate release film-coated tablets. The 10 mg tablet is round (6.0 mm in diameter), biconvex and pale yellow and bears the markings "V" on one side and "10" on the other. The 50 mg tablet is oblong (14.0 x 8.0 mm), biconvex, beige and bears the markings "V" on one side and "50" on the other. The 100 mg tablet is oblong (17.2 x 9.5 mm), biconvex, pale yellow and bears the markings "V" on one side and "100" on the other.

The three strengths are dose proportional The composition of the venetoclax tablets includes venetoclax, copovidone, colloidal silicon dioxide, polysorbate 80, sodium stearyl fumarate, and calcium phosphate dibasic. The composition of the venetoclax film coating includes polyethylene glycol, talc, polyvinyl alcohol, titanium dioxide and either iron oxide yellow (for the 10 mg and 100 rng tablet) or iron oxide yellow, red and black (for the 50 mg tablet).

Venetoclax active substance is an ionisable compound with two pKa values of physiological importance (3.4, acidic sulfonamide and 10.3, basic piperazine). The active substance has very poor aqueous solubility. Because of the very low solubility characteristics, a solid dispersion approach in copovidone (manufacturing an intermediate), is employed to increase the apparent aqueous solubility and bioavailability of venetoclax. The good solubility and compatibility of venetoclax in copovidone was confirmed by DSC studies.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards except for the film coatings, although they are both composed of a mixture of compendial components. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Compatibility of the active substance with the excipients is inferred from the stability studies of venetoclax tablets in blisters.

During formulation development, focus was set on three key requirements for the intermediate the finished tablets: bioavailability, storage stability and manufacturability.

The formulation used in most clinical studies or bioavailability studies is the commercial formulation and has not changed throughout the clinical development except for a small number of batches used in early clinical studies which were not coated (50 mg and 100 mg). Bioequivalence was shown between the coated and uncoated tablets.

A dissolution method has been developed for quality control (QC) during release and stability testing of the finished product. The pH of the dissolution method was fixed at a biorelevant pH 6.8 based on the expectation of substantial drug absorption occurring in the small intestine and the low pH-independent solubility observed at pH 4 and above. The anionic sodium dodecyl sulfate (SDS) was chosen for use in the dissolution medium as it solubilised venetoclax at intestinal pH without affecting its release mechanism. An antifoaming agent was necessary to add immediately before testing. The proposed routine dissolution method operates under sink conditions. The discriminatory power of the dissolution method has been demonstrated. The three strengths of tablets have different dissolution profiles as the release is governed by erosion however available clinical bioavailability data did not indicate a relevant difference in bioavailability between the different tablet strengths.

Pharmaceutical development of the finished product contains QbD elements. A systematic approach has been taken to develop the tablet formulation, manufacturing process and control strategy.

Finished product CQAs were identified based on the quality target product profile (QTPP). Taking into account the physicochemical characteristics of the active substance, the formulation and manufacturing process were developed to achieve desired finished product quality attributes (CQAs). The development was based on prior knowledge and experience of similar products, published literature, design of experiments (DoE) and material characterisation.

An initial risk assessment was performed when the commercial formulation was identified. Critical process parameters (CPP) were identified. The initial risks were assigned based on process understanding gained from approved and marketed products and early development activities. Based on the risks identified, a development plan was devised to systematically generate appropriate data and to identify the manufacturing operating ranges and in-process controls (IPCs). The justification of the critical process parameters (CPP), manufacturing operating ranges and IPCs for the tablets manufacturing processes have been adequately discussed. As the development proceeded, the risk assessment was re-evaluated and updated. In the final risk assessment low residual risks were rated for all parameters. The rationales for the assigned risks have been justified. No design space was proposed. The control strategy is considered satisfactory.

The development and commercial finished product manufacturing sites are described. Dissolution data showed that the quality of the tablets manufactured at different sites is comparable.

The bulk package for venetoclax tablets is described. Bulk stability data have been submitted for two batches of the respective strengths, manufactured at the commercial site, placed in the mentioned package. Results supported the approved bulk holding time.

The primary packaging is PVC/PE/PCTFE aluminium foil blisters. The material complies with EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process for venetoclax, includes manufacture of the intermediate, milling, blending, tableting, coating and packaging. Different manufacturing sites are involved. The process is considered to be a standard manufacturing process as the Applicant has significant prior knowledge of the manufacture of this type of product and has gained significant knowledge of the product during development.

A control strategy for the intermediate venetoclax tablets has been provided. Critical process parameters and in-process controls for the venetoclax intermediate and tablets are described. CPPs and IPCs for the intermediate were established during manufacturing process development to ensure a homogeneous blend and to warrant suitable dissolution of the product. Also, an acceptable level of degradation products is aimed at. For the film coated tablets, CPPs and IPCs have been established to ensure the CQAs assay, uniformity of dosage units and appearance. The target and proven acceptable ranges (PAR) are specified for each CPP. The CPPs and IPCs are adequate for this type of manufacturing process.

The analytical methods used in the control of the intermediate have been described and validated. Justification of the specification is based on development data, batch release data, stability data, compendial requirements, and active substance testing. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Formal validation will be performed post-approval. The process validation scheme has been provided and includes three consecutive production scale batches of the intermediate and three consecutive production scale batches per strength of the tablets and is considered acceptable.

Product specification

The finished product specifications include appropriate tests for this kind of dosage form: description (visual), identification (HPLC-RT and HPLC-UV), assay (HPLC-UV), uniformity of dosage units (Ph. Eur.), water content (Ph. Eur.), dissolution (Ph. Eur.) and degradation products (HPLC-UV).

For dissolution, different criteria are proposed for the three strengths (due to the differences in geometry and total mass) and comprise three-point limits which are justified by the dissolution mechanism (erosion). The limits are based on the batch analysis and stability data obtained on several batches. Impurities present at higher level than the qualification threshold according to ICH Q3A were qualified by toxicological studies and appropriate specifications have been set.

Omission of microbiological limits, elemental impurities, crystallinity, residual solvents and genotoxic impurities has been sufficiently justified.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three production scale batches per strength manufactured at the proposed commercial site according to the proposed manufacturing process confirming its consistency and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Sufficient production scale stability data were provided for batches manufactured at the proposed commercial manufacturing site for all three strengths. Stability data were provided for three pilot scale primary batches of the finished product per strength manufactured at the development site. The batches manufactured at the development site and at the proposed commercial manufacturer were respectively stored under long term conditions for up to 24 or 12 months at 30 ºC / 75% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH. The batches are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, assay, degradation products, dissolution, crystal form and water content. Additionally, microbiological quality and water activity were tested initially, after 6 months of accelerated storage and annually in the long term studies. Some changes were made to the analytical methods during stability studies. The changes to the analytical test methods did not affect the interpretation of the stability results. Changes have been described and the validation summaries for the old methods have been provided. The analytical procedures used are stability indicating.

A few out of specification results in the primary stability batches have been described and acceptably explained. These out of specification results are not considered relevant for the assignment of the shelf life and storage condition as the packaging process was improved throughout development. All stability results for the batches manufactured at the proposed commercial manufacturing site met the proposed acceptance criteria.

In addition, one primary batch per strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant changes were observed and therefore, the tablets are not considered to be light sensitive.

Moreover, various stressed studies have also been performed on tablets including temperature excursions (5 ºC, 50 ºC/ 75% RH, 60 ºC / 75% RH), thermal cycling (-20 ºC for 72 hours and then 50ºC/75% RH for 72 hours, cycled three times) and open dish studies. From the results it can be concluded that the product is sensitive to high humidity and temperature conditions when outside its packaging.

Additionally, stability data were provided for two production scale batches of the intermediate stored under long term conditions. The batches are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing. All results are within the specifications.

Based on available stability data, the proposed holding time of 12 months for venetoclax intermediate under the specified storage conditions is acceptable. The applicant's proposal to define the start of shelf life for the finished product as the date when venetoclax intermediate is combined with excipients was accepted as well.

Based on available stability data, the proposed shelf-life of 2 years without any special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Venetoclax active substance, which is synthesized as a crystalline material, has very low solubility in aqueous media at physiologically relevant pH. To obtain satisfactory bioavailability of the finished product, the substance is formulated as an intermediate. The dissolution of venetoclax is also

considered critical and it is important that the water content of the tablets is adequately controlled and that the package satisfactorily protects the product in this respect.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, or for the finished product.

The results of tests carried out, indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

n/a

2.3. Non-clinical aspects

2.3.1. Introduction

A series of in vitro and in vivo investigations have been conducted in order to characterise the primary pharmacology of Venetoclax. *In vitro* tests aimed at biochemical and cellular pharmacological characterisation of venetoclax. *In vivo*, proof-of-concept of venetoclax monotherapy administered at a single dose or at repetitive doses was evaluated. Subcutaneous as well as systemic xenograft models were subjected to venetoclax single-agent therapy.

The set of toxicology studies was designed to support the development of venetoclax for the target indication based on ICH S9 and for future oncology indications outside of the scope of advanced cancer and falling under the ICH M3 (R2). Conduct of an *in vivo* micronucleus study, fertility and early embryonic development studies, and a phototoxicity study, all outside the scope of ICH S9, were endorsed in scientific advice provided in 2013 by the CHMP. The performed studies include repeat-dose studies ranging from 2 weeks to 6 months in mice and 1 week to 9 months in dogs, *in vitro* and *in vivo* genetic toxicology, dose range-finding studies in mice and rats to support dose selection for possible carcinogenicity assessments, embryo-foetal development in female mice and rabbits, fertility and early embryonic development in male and female mice, dose range-finding in juvenile mice, and phototoxicity in hairless mice. Other studies were *in vitro* genetic toxicity testing of the major human metabolite (M27) and *in vitro* and *in vivo* impurity qualification.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Biochemical Characterization (study R&D/10/905)

TR-FRET (time-resolved fluorescence resonance energy transfer) binding assays were used to assess the binding affinity of venetoclax for Bcl-2, Bcl-XL, Bcl-w, and Mcl-1. Table 1.

Table 1: Binding affinity of Venetoclax

Target	Affinity, K_i, nM
Bcl-2	<0.10
Bcl-X_L	48
Blc-w	245
Mcl-1	>444

Cellular characterization

In Study R&D/10/905 venetoclax was tested against murine FL5.12 cells engineered to be dependent on either Bcl-2 or Bcl-X_L for survival upon interleukin-3 (IL-3) withdrawal and in a cellular mammalian two-hybrid assays to determine its effectiveness at disrupting complexes between anti-apoptotic family members (Bcl-2, Bcl-X_L, or Mcl-1) and BH3-only pro-apoptotic proteins (Bim, Bcl-XS, or Noxa, respectively,Table 2 and Table 3).

Table 2: Cell Viability

Functional selectivity	Results (EC_{50}, uM)
FL5.12-Bcl-2	0.004
FL5.12-Bcl-XL	0.261

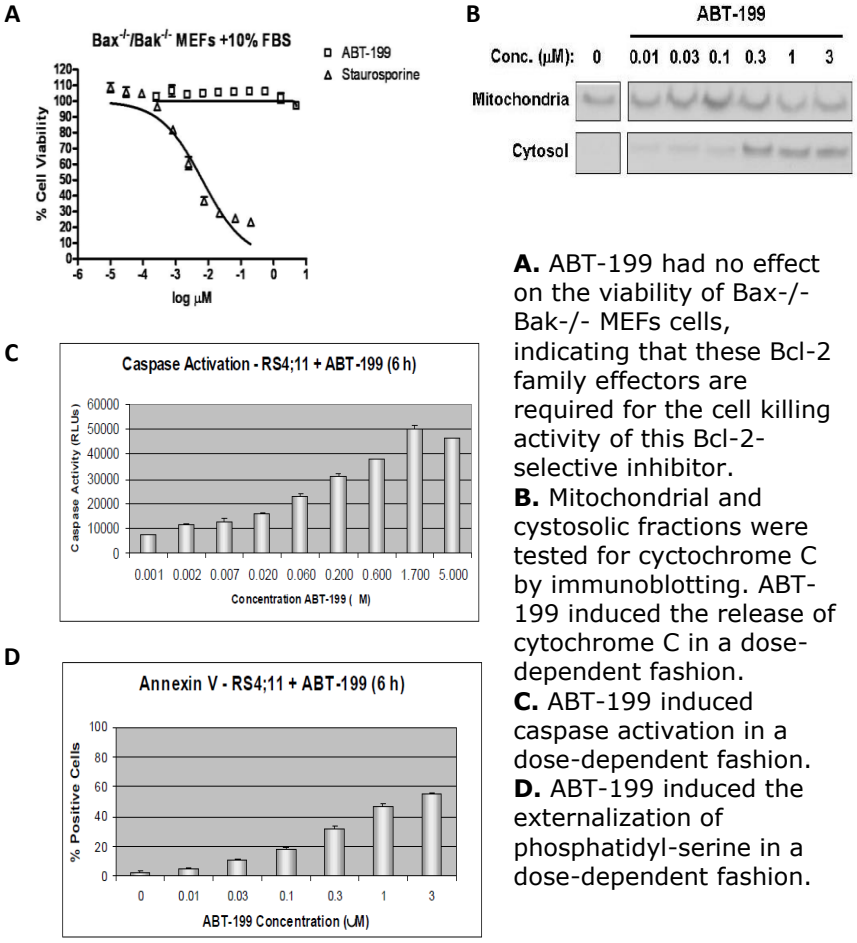
Table 3: Functional activity

Functional Activity	Results, (IC_{50}, uM)
Bcl-2-Bim Mammalian Two-Hybrid	0.003
Bcl-XL-Bcl-XS Mammalian Two-Hybrid	2.167
Mcl-1-Noxa Mammalian Two-Hybrid	>3.000

A variety of assays were carried out to determine whether ABT-199 acts on mechanism to induce the intrinsic apoptotic program

Figure 3.

Figure 3: Mechanism of action



A. ABT-199 had no effect on the viability of Bax-/- Bak-/- MEFs cells, indicating that these Bcl-2 family effectors are required for the cell killing activity of this Bcl-2-selective inhibitor.
B. Mitochondrial and cystosolic fractions were tested for cyctochrome C by immunoblotting. ABT-199 induced the release of cytochrome C in a dose-dependent fashion.
C. ABT-199 induced caspase activation in a dose-dependent fashion.
D. ABT-199 induced the externalization of phosphatidyl-serine in a dose-dependent fashion.

In studies R&D/10/1025, R&D/13/316 and R&D/12/538 Venetoclax exhibited activity against patient-derived CLL cells treated ex vivo, killing these cells with an average EC_{50} of 6 nM (n = 35). Venetoclax was equally potent against CLL samples bearing the 17p deletion, with an average EC_{50} of 8 nM (n = 5), indicating that it may have utility in treating patients with this high-risk lesion. Venetoclax induced killing of primary patient-derived AML cells with a median IC_{50} of 10-20 nM (n = 57). Quantitative immunoblotting of Bcl-2 family members revealed that venetoclax was particularly potent against cell lines expressing high levels of Bcl-2.

In most cases these cell lines were positive for the t(14;18) translocation that drives high level expression of Bcl-2 from the immunoglobulin heavy chain enhancer. Bcl-2 protein levels and the t(14;18) translocation thus represent potential predictive biomarkers for sensitivity to venetoclax. Venetoclax inhibited the viability of multiple myeloma cell lines and primary patient samples bearing the t(11;14) translocation. Venetoclax combined with the proteasome inhibitor bortezomib demonstrated synergistic inhibition in certain multiple myeloma cell lines. These data indicate that venetoclax may have clinical utility as a single agent in patients with t(11;14)-positive multiple myeloma and in additional patients when combined with bortezomib. Data not shown.

Binding affinity and cellular activity of the M27 metabolite (study A-1195425)

To assess the biological activity of A-1621332 a binding assays with three Bcl-2 family proteins and effects on cell viability assays in two human tumour cell lines were performed. Table 4.

Table 4: In vitro potency of ABT-199 and A-1621332.

Compound	Human serum	Biochemical assay (K_i) (uM)			Cell viability (EC_{50}) (uM)	
		Bcl-2	Bcl-X_L	Mlc-1	RS4; 11 cells	Molt-4 cells
ABT-199	0	<0.0001	0.0094	>0.44	-	-
	10	0.0024	>0.42	>0.41	0.058	>9.9
A-1621332	0	0.0022	>0.56	>0.33	-	-
	10	0.14	>0.66	>0.44	>10	>10

Overexpression of Bcl-2 is a major contributor to the pathogenesis of some lymphoid malignancies; antagonism of the action of this protein may enhance response to therapy and overcome resistance. Aberrant expression of Bcl-2 is common in CLL and CLL cells typically have a fundamental reliance on Bcl-2 for survival. Venetoclax has been developed as a selective inhibitor to Bcl-2.

In vitro

Biochemical characterization

Venetoclax exhibits sub-nanomolar affinity for Bcl-2 (Ki <0.010 nM), it binds >4,800-fold and >20,000-fold less avidly to Bcl-XL and Bcl-w, respectively. The M27 metabolite (A-1621332) binds to Bcl-2 with a Ki of 2.2 nM (>220-fold lower than venetoclax) and shows lower affinity to Bcl-XL and Mcl-1 (Ki >560 nM, >330 nM, respectively). M27 is not effective in killing either the Bcl-2-dependent or Bcl-XLdependent tumour cell lines (concentration required for 50% effect [EC50] >10,000 nM).

Cellular assays

Venetoclax potently killed FL5.12-Bcl-2 cells (EC_{50} 4 nM), it showed much weaker activity against FL5.12-Bcl-XL cells (EC_{50} 261 nM), indicating that this compound is functionally selective for Bcl-2. Venetoclax disrupted Bcl-2-Bim complexes further demonstrating the selectivity of the compound.

Venetoclax was ineffective against murine embryonic fibroblasts from transgenic mice lacking Bax and Bak, indicating that this compound does not kill cells through some other off-target mechanism.

Venetoclax induces key hallmarks of apoptosis, including cytochrome C release, caspase activation and the externalization of phosphatidylserine as measured by Annexin V staining.

Venetoclax exhibited activity against patient-derived tumour cells treated ex vivo, killing CLL cells (including cells bearing the high-risk 17p deletion). Venetoclax also demonstrated killing of MM cell lines and primary tumour samples bearing the t(11;14) translocation (such cells tends to express high levels of Bcl-2 relative to Mcl-1). M27 is not effective in killing either the Bcl-2-dependent or Bcl-XLdependent tumour cell lines.

In vivo

To evaluate the efficacy of venetoclax monotherapy administered at a single dose or at doses in vivo, murine models with xenografted human tumour cells were developed in immunocompromised (severe combined immunodeficiency [SCID] or SCID-beige) mice. (

Table 5)

Table 5: In vivo characterization

Model, Study nr	Dose, administration, Species, Gender per group	Findings
Human Acute Lymphocytic Leukaemia, Human Diffuse Large B-Cell Lymphoma, Human Mantle Cell Lymphoma or Human Multiple Myeloma murine xenograft, R&D/10/889	12.5, 25, 50, 100 mg/kg/day, mouse, 10F/grp	**RS4; 11**: Doses of 100, 50, 25 and 12.5 mg/kg/day significantly inhibited tumour growth (90%, 79%, 64% and 36%, respectively) and delayed time to 1 g tumour size by 152%, 107%, 81% and 26%, respectively. Increasing the number of daily administrations augmented the efficacy. Distribution of the daily dose does not offer an advantage over single daily dose. **DoHH-2**: Doses of 100 and 50 mg/kg/day significantly inhibited tumour growth by 51 and 54%, respectively, and delayed time to reach 1 g tumour size by 43% and 50%, respectively. **Granata-519**: Doses of 100 and 50 mg/kg/day significantly inhibited tumour growth by 22 and 28% respectively, and delayed time to reach 1 g tumour size by 56% at both doses. **OPM-2**: Doses of 100 and 50 mg/kg/day significantly inhibited tumour growth by 59% and 70% respectively, and delayed time to reach 1 g tumour size by 86% and 86%, respectively. The minimum efficacious exposure was defined as the exposure that yields a tumour growth inhibition of 70%. This exposure corresponded to an AUC ≥28.8 µg•h/mL and a Cmax >2.7 µg/mL and was reached following a single dose of 25 mg/kg venetoclax.
Toledo non-Hodgkin's Lymphoma Xenograft, R&D/10/975	50, 100 mg/kg/day, mouse, 10F/grp	Doses of 100 and 50 mg/kg/day significantly inhibited tumour growth by 107 and 92%, respectively.
SU-DHL-4 non-Hodgkin's Lymphoma Xenograft, R&D/10/974	100 mg/kg, mouse, 5F/grp	Induced tumour growth inhibition of 66%.

Given as a single-agent, venetoclax inhibits subcutaneous xenograft growth of human tumour cell lines derived from AML (MOLM-13), ALL (RS4;11) and NHL (Toledo). Venetoclax is efficacious using various doses and regimens.

Secondary pharmacodynamic studies

Venetoclax and the M27 metabolite were evaluated in a battery of radioligand binding screening assays that contained representatives of most G-protein coupled receptors and a set of ligand andvoltage-gated ion channel binding sites. Table 6.

Table 6: Secondary pharmacology

System	Concentration/doses	Findings	Study number
ABT-199 binding to Receptors, ion channels and transporters	0.1-10 uM	Displacement of control specific binding by >50% at the adenosine-3 (A3), norepinephrine transporter, dopamine-5 (D5), PPARγ, prostacyclin (IP) (Ki 0.81 µM), peripheral benzodiazepine (BZD) (Ki 0.38 µM), and serotonin-5a (5-HT5a) receptors (Ki 0.37 µM).	R&D/10/833 R&D/10/834 R&D/15/0024 R&D/10/835 R&D/15/0122 R&D/15/0123
M27 metabolite (A-1621332) binding to Receptors, ion	0.03-30 uM	Displacement of control specific binding by > 50% at the melatonin-2 (MT2) (Ki > 30 µM), estrogen (ERα), and delta-opioid (DOP) receptors (Ki 0.65 µM). In follow-up dose response studies, only the	R&D/14/1267 R&D/15/0007 R&D/15/0025

channels and transporters	DOP receptor had Ki values more potent than 30 µM (Ki 0.65 µM). In an additional functional assay, agonist or antagonist activity was not potent enough to calculate an EC_{50} or IC_{50} at the DOP receptor up to a maximum concentration of 10 µM.

Safety pharmacology programme

Venetoclax was evaluated for potential effects on the cardiovascular, respiratory, and central nervous systems *in vitro* and/or *in vivo*. Table 7.

Table 7: Safety pharmacology

Type of study, GLP, Study no	Species, Gender and no/grp	Method of Admin, Duration of dosing	Doses (mg/kg) or concentrations	Safety pharmacology findings
Irwin, non-GLP, R&D/09/1365	Rat, 4M/grp	Oral	3, 10, 30, 100 mg/kg	No effects (plasma concentration of 6.3 µg/mL at 100 mg/kg)
Pro-/Anticonvulsant Effects, non-GLP, R&D/09/1365	Rat, 20M/grp	Oral	3, 10, 30, 100 mg/kg	No consistent effects in the pentylenetetrazole-induced seizure assay.
Spontaneous Locomotor Activity, non-GLP, R&D/09/1365	Rat, 10M/grp	Oral	3, 10, 30, 100 mg/kg	No effects
Functional Observational Battery (FOB), GLP, R&D/10/315, R&D/10/342	Mouse, 8F/grp	Oral	50, 200, 600 mg/kg	No effects through 600 mg/kg (C_{max} 9.4 µg/mL)
hERG, non-GLP, R&D/10/795	In vitro	NA	1.5 ug/ml	13.3% reduction at the solubility limited concentration of 1.5 µg/mL.
Cardiovascular, non-GLP, R&D/10/766	Anesthetized Dog, 6M/grp	Iv	0.003, 0.110, 0.333 mg/kg/min	Venetoclax produced a statistically significant reduction (-6%) in dP/dtmax at a plasma concentration of 16.2 µg/mL and a reduction (-11%) in cardiac output at a plasma concentration of 32.4 µg/mL. No effect on MAP, HR, CO, dP/dt_{max}, LVEDP, CVP, PAP, PVR, SVR, QTcV or PR interval through the highest plasma concentration of 46 µg/mL.
Cardiovascular, GLP, R&D/10/318	Conscious Dog, 6M/grp	Oral	5, 50, 150 mg/kg	No effect on MAP, HR, body temperature or QTc through 150 mg/kg (plasma concentration 15.7 µg/mL).
Respiratory, GLP, R&D/10/317, R&D/10/342	Mouse, 8M/grp	Oral	50, 200, 600 mg/kg	No effect on respiratory rate, tidal volume or minute volume through 600 mg/kg (Cmax 7.8 µg/mL).

2.3.3. Pharmacokinetics

Absorption

The pharmacokinetic profile of venetoclax in mouse, rat, dog and monkey was characterized by low plasma clearance values in monkey (0.27 L/hr*kg), rat (0.22 L/hr*kg), and mouse (0.14 L/hr*kg), with much lower values in dog (0.02 L/hr*kg). The compound was characterized by moderate to low volumes of distribution (Vss) in all species, with values ranging from 0.30 to 0.87 L/kg for mouse, dog, monkey and rat. The apparent elimination half-life ranged from 2.2 hr in monkey to approximately 12 hr in dog. Oral bioavailability from a PEG-400 solution formulation was low and ranged from 8.6% in monkey to 27.8% in dog.

Distribution

Following intravenous administration to male CD-1 mice, radioactivity was well distributed into liver, kidneys, lungs, mesenteric lymph nodes and mandibular lymph nodes, while poor distribution was observed in adipose tissue. At 0.5 hr post dose, the highest radioactivity was found in liver, followed by lungs, mesenteric lymph nodes, mandibular lymph nodes, kidneys and adipose tissue. The maximum radioactivity was observed at 2 hr post dose for liver, kidneys and mesenteric lymph nodes, while at 1 hr post dose for lungs and 6 hr post dose for mandibular lymph nodes and adipose tissue. No tissue-specific retention of radioactivity was observed and radioactivity decreased after reaching maximal concentrations.

In pigmented Long-Evans rats radioactivity was absorbed from an oral dose and distributed into tissues, with peak concentrations occurring at 4 hr post dose in most tissues. The rapid decline and elimination of radioactivity from the uveal tract and pigmented skin observed for both male and female rats illustrated that there was no evidence of selective association with the melanin-containing tissues of the pigmented rat. Concentrations of radioactivity in eye lens and the non-circumventricular central nervous system tissues were below measurable levels throughout the course of this study.

Venetoclax is very highly protein bound, independent of concentration, with unbound fraction values <0.01. M27 is also highly protein bound in mouse, rat, dog, monkey and human. Venetoclax and M27 do not partition preferentially into the blood cellular compartment.

Metabolism

Biotransformation of venetoclax in nonclinical species (mouse, rat, rabbit, dog) and human involves enzymatic oxidation on the dimethyl cyclohexenyl moiety to form M2, M3, M4 and M5. Also downstream metabolites are formed by further oxidation. In general, all human metabolites were also identified in at least one non-clinical toxicity species.

In humans, M27 is the major metabolite in plasma, representing 12.0% of total radioactivity after a single oral dose. M27 represents up to 29.4% and 30.6% of venetoclax + M27 exposure at steady state in CLL or NHL patients who received a final dose of 400 and 600 mg/day of venetoclax treatment, respectively. M27 is present in plasma of non-clinical toxicology species in vivo at maximal tolerated doses (MTD) but at lower exposure than in human. M27 is not considered a human unique metabolite but is disproportionate. M27 was proposed to be formed via mono-oxidation of venetoclax on the 6-position of the cyclohexenyl moiety to give M5, followed by enzyme-mediated cyclization at the α-carbon of piperazine.

Excretion

Following oral administration of venetoclax to nonclinical species and humans, parent compound and metabolites were mainly cleared via biliary excretion and fecal elimination, with minimal renal clearance. In mice, 93.6% of an oral dose was eliminated in feces, with 0.6% of the dose recovered in the urine. In bile cannulated rats, 92.8% of an intravenous dose was recovered in the bile, with 0.4% of the dose recovered in the urine. In dog, 87.4% of the dose was recovered in the feces, with minimal renal elimination (0.1% of the dose). In the human radiolabeled mass balance study, a mean of 100% of the dose was recovered in feces, with <0.1% recovered in urine (216 hr collection period).

2.3.4. Toxicology

Single-dose toxicity

A single dose study in dogs was performed primarily to assess the effect and recovery of peripheral blood lymphocytes following a single dose. Generally dose-related decreases in lymphocyte counts were observed. B-cells were the most sensitive lymphocyte subtype based on the magnitude of decrease and the length of time required for recovery. At ≥30 mg/kg, B-cell decreases of more than 90% was observed, and recovery at 18 weeks post treatment. The effect on CD4+ and CD8+ T-cells was slightly less pronounced. A generally dose-responsive decrease was observed at 30 and 100 mg/kg; maximum decreases at 100 mg/kg (were -54% for CD4+ T-cells and -58% for CD8+ T-cells. Recovery for both T-cell types was reached in less than a month, except for CD4+ T-cells in one animal at 100 mg/kg, which required 15 weeks, and in another animal that exhibited partial recovery. Overall, the time needed for recovery of peripheral blood lymphocyte decreases after a single dose was similar to that after 2 weeks of once daily dosing in dogs.

Table 8: Summary of single-dose toxicity study performed with venetoclax in dogs.

Study ID/GLP/ Duration	Species/Sex/ Number/Group	Dose (mg/kg) /Route	Observed max non-lethal dose	Approx. lethal dose
R&D/12/395 Non-GLP Single dose TK and lymphocyte recovery	Beagle dogs 3 dogs/group (2M+1F/dose or 1M+2F/dose)	2, 5, 30, 100 Oral gavage Test item: Venetoclax: copovidone:vitamin E TPGS solid dispersion, 15:65:20 Vehicle: water	All doses were tolerated	Not established

Noteworthy findings
TK: Mean $AUC_{0\text{-}inf}$ was 24.5, 68.6, 654.9 and 2822.7 µg·h/mL at 2, 5, 30 and 100 mg/kg, respectively.
Peripheral blood lymphocytes: Generally dose-related ↓ in peripheral blood lymphocytes (total and subsets consisting of CD4+ and CD8+ T-cells and CD21+ mature B-cells). B-cells were the most sensitive based on magnitude of effect (>90% decrease at ≥30 mg/kg) and time required for recovery (up to 18 weeks post dose at dosages of ≥5 mg/kg). There was evidence of reversibility within 14 to 18 weeks post dose for total and lymphocyte subsets.

	Dose (mg/kg/day)	Onset of decrease	Time/maximum decrease	Onset of recovery
Lymphocytes	2	-	-	-
	5	24 h	48 h/-36%	504 h
	30	1-24 h	24-48 h/-25 to -58%	168-1176 h
	100	1 h	48 h/-50 to -62%	2016-2352 h
CD4+ T cells	2	-	-	-
	5	-	-	-
	30	1-24 h	24-48 h/-15 to -64%	168-504 h
	100	1-3 h	24-72 h/-49 to -54%	504-2520 h
CD8+ T cells	2	-	-	-
	5	9 h	48 h/-20%	72 h
	30	7-24 h	24 h/-13 to -35%	72-504 h
	100	1-3 h	24-72 h/-53 to -58%	
B cells	2	1 h	24 h/-35 to -65%	48-168 h
	5	1 h	24 h/-68 to -87%	72-3024 h
	30	1 h	24-72 h/-93 to -95%	2520-3024 h
	100	1 h	9-72 h/-91 to -96%	2016 h

Repeat-dose toxicity

The repeat-dose toxicity of venetoclax after oral administration was investigated in studies up to 6 months in mice, and up to 9 months in dogs. The primary toxicities were effects on the haematologic system (decreased lymphocytes and red blood cell mass) in mice and dogs and on the male reproductive system (testicular germ cell depletion) in dogs. Other noteworthy findings in dogs were epithelial single cell necrosis in multiple tissues and hair coat colour change.

Mortality/clinical signs

In mice, there were no remarkable venetoclax-related effects on clinical signs or body weights in any of the performed studies. However, there were a few mouse mortalities of unknown relation to venetoclax treatment. In the 4-week study, 1 male mouse was found dead at 600 mg/kg/day and in the 6-month study, two male mice were found dead, one each at 15 and 300 mg/kg/day, respectively. No significant clinical observations were present in these animals prior to demise and the cause of the death could not be ascertained following macroscopic and microscopic evaluation. Therefore, the relation to venetoclax-treatment is unclear. However, based on the absence of any significant findings apart from those of the on the haematologic system, the deaths are considered as likely incidental.

In dogs, venetoclax administration in the 4-week study was associated with dose-related, transient post-dose emesis, increased salivation and fecal alterations at dosages of ≥5 mg/kg/day. At the highest dose in the 4-week study, mild to moderate signs of swelling of the skin on the ears, head (cranial area) and forepaws and/or hindpaws were observed in 8 of 10 dogs. In three dogs, the swelling reaction was observed after the first dose. The clinical signs were transient and sporadic in occurrence, and were absent during the recovery period. A mechanistic basis for the swelling reactions was not established, but there were no signs of anaphylaxis. In the 9-month dog study, non-adverse decreases in mean body weight and body weight gain, associated with decreases in food consumption, were observed at ≥2 mg/kg/day.

Effects on lymphocytes (mice and dogs)

Venetoclax produced mild to marked, generally dose-related decreases in leukocytes (primarily, lymphocytes) in peripheral blood and in lymphocytes in lymphoid tissues at all dose levels administered to mice from 2 weeks to 6 months and to dogs from 1 week to 9 months. Decreases in peripheral blood lymphocyte counts were similar across dosing periods, with maximum decreases ranging from -69% to -75% in mice, to -64% in rats and to -81% in dogs. Decreased peripheral blood lymphocytes (assessed in dogs) in repeat-dose studies were observed by approximately 24 hours after the first dose and reached a maximum after approximately 2 weeks of dosing. Correlating with decreased peripheral blood lymphocyte counts were minimal to moderate lymphocyte decreases in lymphoid tissues, including the spleen, thymus, lymph nodes, and Peyer's patches/gut-associated lymphoid tissue (GALT). Decreases in peripheral blood lymphocytes exhibited evidence of reversibility in mice and dogs, but the time required for reversibility was considerably longer in dogs (18 weeks) than in mice (4 weeks). Lymphocyte subsets (mature T-cells, helper [CD4+] T-cells, cytotoxic [CD8+] T-cells, and [CD21+] mature B-cells) were assessed in dogs. All lymphocyte subtypes were decreased, with the greatest decreases observed in B-cell counts (>-90%). Similar to total lymphocyte counts, both B-cells and T-cells required up to 18 weeks for reversibility after completion of a 2-week dosing period in dogs. Following 4 weeks of dosing in dogs, reversibility did not occur after a 4-week recovery period.

Effects on red blood cells (mice and dogs)

Dose-related decreases in indicators of red blood cell mass were similar in mice and dogs. Haemoglobin decreases reached -21% in mice at 600 mg/kg/day (AUC_{ss} 91 µg·hr/mL) and -23% in dogs at 150 mg/kg/day (AUC_{ss} 572 µg·hr/mL) following 4 weeks of dosing. Based on magnitude (>20%), these decreases in haemoglobin were considered to be adverse. The corresponding NOAELs were 200 mg/kg/day in mice and 50 mg/kg/day in dogs, corresponding to 1.9- and 14.8-fold the clinical AUC exposure, respectively. In the 4-week studies, decreased red cell mass reversed at the end of the 4-week recovery periods. With increased duration of dosing and lower dosages, dose-related decreases in RBC mass (haemoglobin) were observed in mice (up to -13%) in the 6-month study at ≥50 mg/kg/day (AUC_{ss} ≥9.6 µg·hr/mL); in the 9-month dog study, there were no decreases in haemoglobin, but dose-related reductions were observed in mean corpuscular volume (up to -17%) and mean corpuscular haemoglobin (up to -18%) at ≥6 mg/kg/day (AUC_{ss} ≥52.1 µg·hr/mL). The NOAELs for these effects in the longer duration studies in mice and dogs correspond to exposures of 0.9- and 2.7-fold the clinical AUC, respectively.

Effects on male reproductive organs (dogs)

In dogs, venetoclax caused adverse, non-dose-related microscopic findings in testes at all dose levels administered for 4 weeks (≥5 mg/kg/day) and 9 months (≥2 mg/kg/day). In the 4-week study, these findings consisted of severe decreases in the numbers of spermatogonia, with progression to severe decreases in the numbers of all germ cells in testes during the 4-week recovery period. In the 9-month study, the findings were characterized as moderate to severe bilateral degeneration/atrophy of the seminiferous tubules. In both studies, testes weights were decreased, and in the 9-month study, prostate weights were decreased. The corresponding plasma exposures (mean AUC_{ss}) at 5 and 2 mg/kg/day were 59.3 µg·hr/mL and 15.1 µg·hr/mL, respectively, corresponding to ~1.9- and 0.4-fold the clinical AUC. Mice did not have testicular changes associated with venetoclax administration.

Effects on epithelial tissues (single cell necrosis, dogs)

Single cell necrosis was observed in multiple epithelial tissues of the dog following daily administration of venetoclax from 1 week to 9 months; the lowest AUC values at which these changes were observed were 61 µg·hr/mL, ~2-fold clinical AUC (5 mg/kg/day, 4-week study) and 17 µg·hr/mL, ~0.5-fold the clinical AUC (2 mg/kg/day, 9-month study). Affected tissues were gallbladder epithelium, exocrine pancreas, prostate, epididymides and stomach. These changes were minimal to mild. Reversibility was evaluated in the 4-week study, and was observed in gallbladder and exocrine pancreas, but not in the prostate and epididymides (potentially associated with testicular germ cell loss) or in the stomach. Single-cell necrosis was considered not to be adverse due to its minimal to mild magnitude and because no loss of mucosal integrity was observed microscopically. There were no venetoclax-related findings of single cell necrosis in mice; the maximum achieved AUC_{ss} in mice was 91 µg·hr/mL, corresponding to ~2.9-fold the clinical AUC.

Effects on hair coat colour (dogs)

In the 9-month dog study, a change in colour of the hair coat to white was observed at ≥6 mg/kg/day after approximately 3 months of dosing. The affected hair was initially on the muzzle. From 3 to 9 months of dosing, loss of hair pigmentation progressed from the muzzle to affect the majority of normally darkly pigmented hair and correlated microscopically with decreased pigment in hair follicle bulbs. Physical examinations of the skin (epidermis) and ophthalmic examinations determined that pigmentation of the skin and in the eye (particularly in the pigmented iris and fundus) appeared unaffected. This was confirmed by the absence of associated histopathologic findings in skin (other than in hair follicle bulbs) and in the eye. Hair coat colour change could not be assessed in CD-1 mice

or Sprague-Dawley rats due to the white hair coat in these strains, but a change to gray coat colour was also observed in NZBWF1 mice (lupus model) treated daily with 100 or 33 mg/kg of venetoclax, but not at lower dosages.

Other effects (dogs)

In dogs, non-adverse, minimally increased pigment was observed in Kupffer cells or macrophages in the liver and gallbladder, respectively, at ≥5 mg/kg/day in the four-week study and at ≥2 mg/kg/day in the nine-month study. No corresponding increases in pigment in these or other tissues were observed in mice or rats.

Interspecies comparison

In the 4-week repeat-dose studies, the AUC exposure multiples at the highest dose levels compared to the clinical AUC were ~2.9-fold in mice and ~18-fold in dogs. In the longer duration studies, the AUC exposures were around the clinical exposure in mice and ~2.7-fold dogs.

Genotoxicity

The genotoxic potential of venetoclax was evaluated in a series of non-GLP and GLP *in vitro* and *in vivo* studies as summarised below. Venetoclax was tested negative in a complete package of genotoxicity studies including test for gene mutations and chromosomal aberrations *in vitro* and chromosomal aberrations *in vivo*.

Table 9: Summary of *in vitro* and *in vivo* GLP genotoxicity studies performed with venetoclax.

Type of test/ study ID/ GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
Gene mutations in bacteria R&D/10/420 GLP	*S. typhimurium* TA98, TA100, TA1535, TA1537 *E. coli* WP2 *uvr*A	*Range-finder* ±S9: 5, 10, 50, 100, 500 and 5000 µg/plate *Mutagenicity test* ±S9: 5, 10, 50, 100, 500 and 5000 µg/plate	Adequate positive and negative controls produced expected effects. *Range-finder* Cytotoxicity (>50% reduction in revertant counts) was observed with TA1537 at 5000 µg/plate +S9. Precipitates at ≥500 µg/plate ±S9 with all tester strains. *Mutagenicity test* No mutagenicity up to the highest dose tested. **Negative**
Chromosomal aberrations R&D/10/421 GLP	Human peripheral lymphocytes	*Range-finder* ±S9: 1.17, 2.34, 4.69, 9.38, 18.8, 37.5, 75.0, 150, 300, 600 and 1200 µg/mL, cells treated for 3 hrs -S9: 1.17, 2.34, 4.69, 9.38, 18.8, 37.5, 75.0, 150, 300, 600 and 1200 µg/mL, cells treated for 22 hrs *Chromosomal aberration test* -S9: 6.00, 9.00, 12.2, 17.5, 20.7, **24.0**, 26.5, **29.8**, 35.0 and **50.0** µg/mL, cells treated for 3 hrs. -S9: 4.00, 6.00, 9.00, **12.2**, 15.0, **17.6**, **20.7**, 24.0, 26.5, 32.0 and 40.0 µg/mL, cells treated for 22 hrs +S9: 9.00, 12.2, 17.5, 26.5, 32.0, 35.0, **40.0**, **45.0**, **50.0** and 70.0 µg/mL, cells treated for 3 hrs. Bold concentrations assessed for chromosomal aberrations.	Adequate positive and negative controls produced expected effects. *Range-finder* ±S9, 3 hrs and -S9, 22 hrs: Cytotoxicity at ≥37.5 µg/mL, precipitation at ≥150 µg/mL. *Chromosomal aberration test* -S9, 3 hrs: Cytotoxicity at 50 µg/mL (51% reduction in MI), negative. -S9, 22 hrs: Cytotoxicity at 20.7 µg/mL (51% reduction in MI), negative. +S9, 3 hrs: Cytotoxicity at 50 µg/mL (51% reduction in MI). A small increase in the number of chromatid exchanges (triradials and quadriradials) at 50 µg/mL. The increase was statistically insignificant and within the historical control value. Therefore, the low level of chromatid exchanges observed are not considered to have any biological relevance. **Negative**
Chromosomal aberrations R&D/12/675 GLP	CD1 mice, micronuclei in bone marrow 5/sex/group + satellites for TK	0 (placebo), 0 (vehicle), 208.8, 417.5, and 835 mg/kg. Oral gavage, single dose Test item: Venetoclax: Tween 80: copovidone: colloidal SiO2 (12:7:80:1 w/w/w) Placebo control: Tween 80: copovidone (7:93 w/w) Vehicle: 0.1% antifoam C in water Bone marrow sampled at 24 hrs in all test groups and additionally at 48 hrs in placebo and vehicle controls and high dose groups At least 2000 PCEs/animal were evaluated. Cytotoxicity was assessed by scoring the number of PCEs and NCEs in at least 500 erythrocytes on the slide.	Adequate positive and negative controls produced expected effects. TK: Mean AUC was 106/159, 127/184 and 179/278 µg·h/mL in M/F at 208.8, 417.5, and 835 mg/kg, respectively. Mortality: None. Micronucleus assay: Venetoclax did not induce statistically significant increases in micronucleated PCEs at any dose except in F at 835 mg/kg. However, this increase was not considered to be biologically significant since the % micronucleated PCEs from the high dose females (0.14%) were within historical control values (0.00 to 0.15%). Venetoclax was cytotoxic to the bone marrow at 417.5 and 835 mg/kg in males and at 835 mg/kg in females. The micronucleated PCEs observed in the vehicle control group were within the historical control range for males (0.02± 0.03% and 0.07±0.06% for the 24- and 48-hour time points, respectively) and females (0.03±0.03% and 0.03±0.04% for the 24- and 48-hour time points, respectively). **Negative**

Carcinogenicity

No carcinogenicity studies were performed which in view of the applied indication is acceptable and in agreement with recommendations in ICH S9. To support future indications outside the scope of S9, dose range-finding studies in wild type littermates of Tg.rasH2 mice (up to 4 weeks) and in Sprague Dawley rats (up to 13 weeks) were performed to enable dose selection for possible carcinogenicity assessments. The primary toxicity in rats was similar to that previously observed in mice and dogs, i.e. effects on the haematological system (decreased lymphocytes and red blood cell mass).

Fertility, early embryonic development and reprotoxicity

In fertility and early embryonic development studies conducted in male and female mice there were no effects on fertility, pregnancy (implantation), ovarian and uterine parameters, male or female reproductive organs, or on female estrus cycling. The NOAEL for males and for females was 600 mg/kg/day, corresponding to 2.7- and 3.1-fold the clinical AUC, respectively. However, in repeat-dose toxicology studies, venetoclax caused irreversible testicular germ cell depletions in dogs at exposures below the clinical AUC exposure, suggesting a risk for irreversible infertility in male patients treated with venetoclax.

Embryo-fetal development toxicology studies were conducted in pregnant mice and rabbits.

In the mouse DRF study a pronounced embryo-foetal toxicity was observed, i.e. a dose-related increased post-implantation loss up to about 90% at the highest dose corresponding to about 2 times clinical exposure and in the absence of overt maternal toxicity. In the pivotal mouse study, findings were limited to the top dosage of 150 mg/kg/day, and consisted of (1) increased post-implantation loss (associated with an increase in early resorptions and corresponding decreases in litter size and numbers of live foetuses per litter) and (2) decreased foetal body weight. There were no venetoclax-related fetal external, soft-tissue, or skeletal malformations or variations. The NOAEL for mouse maternal toxicity was 150 mg/kg/day, corresponding to 1.1-fold the clinical AUC, and the NOAEL for mouse embryo-foetal toxicity was 50 mg/kg/day, corresponding to 0.8-fold the clinical AUC.

In the rabbit study, 4 dams were found dead or euthanized at the highest dose tested, 300 mg/kg/day. These early deaths were preceded by adverse clinical signs, maternal body weight losses and severely reduced food consumption and necropsy revealed gross abnormalities in the GI tract in three out of the four dams. The mean AUC at 300 mg/kg/day on GD19 was 4900 ng·h/mL corresponding to ~0.1 fold the clinical AUC. Despite the maternal toxicity, there were no effects on reproductive parameters (e.g., post-implantation loss) or foetal parameters (e.g., external, visceral, or skeletal development). The NOAEL for maternal toxicity was 100 mg/kg/day, corresponding to 0.07-fold the clinical AUC, and NOAEL for embryo-foetal development was 300 mg/kg/day, corresponding to 0.2-fold the clinical AUC.

Local tolerance

No dedicated local tolerance studies were performed. The local tolerance after oral administration is considered adequately assessed in performed oral repeat-dose toxicology studies.

Other toxicity studies
Phototoxicity

Venetoclax absorbs ultraviolet light between 200 and 390 nm and in the visible spectrum from 400 to <500 nm with MEC values above the threshold value. Poor distribution of [^{14}C]-venetoclax to the eyes and to both pigmented and non-pigmented skin was observed following a single oral dose to Long Evans rats. Based on the light absorbance, the phototoxic potential of venetoclax was evaluated in a 3-day *in vivo* phototoxicity study using hairless female mice. In this study, no indications of phototoxicity

in skin were evident at doses ≤825 mg/kg/day. Therefore, venetoclax is considered to have a low phototoxic potential.

Metabolites

Metabolite M27 was identified as a major metabolite of venetoclax in humans representing ~12% of the total plasma radioactivity in the human mass balance study. M27 was not mutagenic in the Ames test and nor was micronucleus induction observed in the *in vitro* micronucleus test in peripheral lymphycytes. M27 was present in both mice and dogs at the maximum tolerated dose, but at much lower exposure than in humans. The mean gender combined AUC exposure to M27 in 5-days repeat-dose studies in mice and dogs was 0.76 and 1.27 µg·h/mL, respectively, which represent approximately 5 and 9%, respectively, of the exposure observed in humans (geometric mean $AUC_{ss,24}$ = 14.1 µg·h/mL) at 400 mg venetoclax.

Impurities

The drug substance impurities A-1470045.0, A-1258315.0, A-1550366.0 and A-1550367.0, and the drug product degradants A-1548065.0 and A-1548068.0 are all considered adequately qualified at the proposed specification levels. The control strategy for the genotoxic or potentially genotoxic and carcinogenic impurities are considered as adequate.

2.3.5. Ecotoxicity/environmental risk assessment

Table 10: Summary of main study results

Substance (INN/Invented Name): Venetoclax			
CAS-number (if available): 1257044-40-8			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD123	Log P_{ow} = 5.79 at pH 4 Log P_{ow} = 5.91 at pH 7.4 Log P_{ow} = 4.77 at pH 9	Potential PBT (Y)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	Log P_{ow} = 5.79 at pH 4 Log P_{ow} = 5.91 at pH 7.4 Log P_{ow} = 4.77 at pH 9	
	BCF	BMF = 0.0048 kg/kg	Not B
Persistence	ready biodegradability	-	
	$DegT_{50}$	$DT_{50, water}$ = 17/23 d (r/r) $DT_{50, sediment}$ = 367/121 d (r/r) $DT_{50, system}$ = 185/100 d (r/r) $DT_{50, soil}$ = 981/981/669/278 d	r=river; DT_{50} values corrected to 12°C. Conclusion: vP
Toxicity	NOEC algae NOEC crustacea NOEC fish	TBD TBD TBD	T/not T
	CMR	not investigated	Potentially T
PBT-statement :	Venetoclax is considered not to be PBT, nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$	2.0 (default) 0.07 (refined)	µg/L µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)	not investigated		
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106 or …	TBD	Water solubility information

					requested
Ready Biodegradability Test	OECD 301	-			Not reported
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 7.8/11 d (r/r) $DT_{50, sediment}$ = 173/53 d (r/r) $DT_{50, system}$ = 87/47 d (r/r) % shifting to sediment = 85-98%			r=river; DT_{50} values at 20°C; Significant shifting to sediment observed.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata*	OECD 201	NOEC	TBD	µg/L	Water solubility information requested
Daphnia sp. Reproduction Test	OECD 211	EC10	3.3	µg/L	Reproduction
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC	TBD	µg/L	Water solubility information requested
Activated Sludge, Respiration Inhibition Test	OECD 209	EC10	>1000	mg/L	Respiration
Phase IIb Studies					
Bioaccumulation/ *Lepomis macrochirus*	OECD 305	BMF	0.0048	kg/kg	Dietary test; growth corrected; lipid normalized BMF
Aerobic and anaerobic transformation in soil	OECD 307	<u>Sandy loam soil</u> DT50 = 462 days 0.9% CO_2 <u>Clay loam soil</u> DT50 = 462 days 1.0% CO_2 <u>Sandy loam soil</u> DT50 = 315 days 1.2% CO_2 <u>Sandy soil</u> DT50 = 131 1.2% CO_2		days	Determined at 20°C
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	+75% effect +81% effect +340% effect +512% effect	50 100 500 1000	mg/kg mg/kg mg/kg mg/kg	Nitrification rate
Terrestrial Plants, Growth Test/ *Allium cepa*; *Brassica napus*; *Glycine max*; *Lolium perenne*; *Zea mays*	OECD 208	NOEC	≥100	mg/kg	Survival; emergence; shoot weight
Terrestrial Plants, Growth Test/ *Phaseolus vulgaris*	OECD 208	NOEC NOEC	≥100 <100	mg/kg mg/kg	Survival; emergence shoot weight
Earthworm, Acute Toxicity Tests/ *Eisenia fetida*	OECD 207	LC50,EC50	>100	mg/kg	Mortality; weight
Collembola, Reproduction Test/ *Folsomia candida*	ISO 11267	NOEC	≥100	mg/kg	Survival; reproduction
Sediment dwelling organism/ *Chironomus riparius*	OECD 218	NOEC	≥433	mg/kg	Emergence; development; normalised to 10% o.c.

TBD = to be determined

Venetoclax is considered not to be persistent, bioaccumulative and toxic (PBT), nor very persistent, very bioaccumulative (vPvB). A risk to the sewage treatment plant (STP) is not anticipated based on the prescribed use of venetoclax. It is noted that the methodology used to calculate the $PEC_{sediment}$ and PEC_{soil} in the ERA as in accordance to the Q&A document (EMA/CHMP/SWP/44609/2010) q6 and section 5.3.3 of the ERA guideline (EMEA/CHMP/SWP/4447/00 corr 2) where reference is made to the proper methodology for $PEC_{sediment}$ and PEC_{soil} calculations using $K_{oc, sludge}$.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the

CHMP recommends the following points to be addressed:

- To correct the PEC calculation in the environmental risk assessment.

2.3.6. Discussion on non-clinical aspects

The binding and inhibition data show that Venetoclax is a selective inhibitor of Bcl-2. The data also show that Venetoclax increases the percentage of apoptotic cells and induces cell death of patient derived cancer cells. This increase in apoptosis was shown to be dependent on functional Blc-2. In murine proof-of-concept models venetoclax showed inhibition of subcutaneous xenograft growth of human tumour cell lines.

The major human metabolite, M27, was assessed for Bcl-2 binding and effect on cell viability. The data show that M27 was able to bind to Bcl-2 with about 220-fold lower affinity than venetoclax. In addition, M27 was unable to induce apoptosis in treated cells.

At plasma concentrations of ≥16 µg/mL in anesthetized dogs Venetoclax produced mild reductions in myocardial contractility. This effect was not observed in conscious dogs. The therapeutic dosage of venetoclax is 400 mg/day for the target indication and is associated with average steady state plasma exposures of 2.1 µg/mL (C_{max}). The exposures reached in the safety pharmacology studies are considered to be sufficient. In general, the non-clinical data show a negligible risk for QT/ECG effects at clinical exposures, effect on QT was also addressed in the clinical study M12-175 (see clinical safety).

The PK profile of venetoclax show low plasma clearance and moderate to low volume of distribution in all species tested. Venetoclax elimination half-life ranged from 2.2 hours in monkey to 12 hours in dog with a bioavailability ranging from 8.6% to 27.8%. Venetoclax showed distribution into tissues with peak concentration after 4 hours. No tissue-specific retention was observed, including pigmented tissues. Venetoclax did not distribute to the CNS.

Biotransformation of venetoclax in nonclinical species (mouse, rat, rabbit, dog) and human involves enzymatic oxidation on the dimethyl cyclohexenyl moiety. In humans, M27 is the major metabolite in plasma, representing 14.0% of total radioactivity after a single oral dose. M27 is present in plasma of non-clinical toxicology species in vivo at MTD but at considerably lower exposure than in human. M27 is not considered a human unique metabolite but is disproportionate.

Following oral administration of venetoclax to nonclinical species and humans, parent compound and metabolites were mainly cleared via biliary excretion and fecal elimination, with minimal renal clearance.

Venetoclax produced mild to marked, generally dose-related decreases in leukocytes (primarily, lymphocytes) in peripheral blood and in lymphocytes in lymphoid tissues, with maximum decreases in peripheral blood ranging from -69% to -75% in mice, to -64% in rats and to -81% in dogs. The observed lymphocyte decreases are an expected effect of Bcl-2 inhibition. The lymphocyte decreases in lymphoid tissues were not as pronounced as in peripheral blood. In the 39-week dog study, minimal to mild decreases in lymphocytes were observed in Peyer's patch, mesenteric and mandibular lymph nodes, whereas no effects were noted in thymus, spleen, and popliteal and tracheobronchial lymph nodes. In the 26-week mouse study, lymphocyte decreases among lymphoid tissues were minimal to moderate.

Despite the substantial decrease of lymphocytes in peripheral blood and to lesser extent in lymphoid tissues, venetoclax did not cause an apparent impaired immune function at the level of challenge encountered in laboratory housing (see also clinical safety).

Dose-related decreases in indicators of red blood cell mass were similar in mice and dogs and the NOAELs for these effects in the longer duration studies correspond to exposures 0.9- and 2.7-fold the clinical AUC, in mice and dogs, respectively. Decreased haemoglobin and/or anaemia have also been observed in patients. Decreases in red cell mass are readily monitored by routine haematology analysis in patients and the non-clinical data suggest that the effects are reversible. Both Bcl-2 and Bcl-X_L are speculated to be involved in the decreased RBC mass. Although venetoclax is highly selective for Bcl-2 (Ki <0.010 nM), it could exert a slight effect on Bcl-X_L (Ki 48 nM). Bcl-X_L is essential for maturation and survival of erythroid cells, particularly at the later stages. However, studies have also indicated that erythropoietin control of Bcl-2 during proliferation and differentiation contributes to the viability of erythroid progenitor cells. Therefore, on-target pharmacologic inhibition of Bcl-2 by venetoclax could play a role in the observed decreases in red cell mass. Bcl-X_L is also important for haeme synthesis and silencing of Bcl-X_L expression in experimental models greatly decreased haemoglobin synthesis.

Minimal to mild single cell necrosis was observed in multiple epithelial tissues (gallbladder epithelium, exocrine pancreas, prostate, epididymides and stomach) of the dog following daily administration of venetoclax from 1 week to 9 months. Reversibility was observed in gallbladder and exocrine pancreas, but not in the prostate and epididymides (potentially associated with testicular germ cell loss) or in the stomach. The epithelial single cell necrosis was not associated with other signs of organ toxicity such as inflammation or disrupted tissue architecture. The nature of the finding seems consistent with apoptosis although this was not confirmed by dedicated staining techniques. As bcl-2 is known to be expressed in various epithelia, the finding is considered likely due to the pharmacological action of venetoclax. Although the clinical significance of the epithelial single cell necrosis in unclear, based on the magnitude of effect and lack of associated toxicity, no serious or adverse effects on epithelial tissues are expected in the clinical situation.

In the 9-month dog study, a change in colour of the hair coat to white was observed after approximately 3 months of dosing. The effect on hair coat colour is considered a likely effect of Bcl-2 inhibition. Evidence from Bcl-2 knock-out mouse (Bcl-2 $^{-/-}$) studies indicates that hair hypopigmentation occurs due to loss of hair follicle melanocytes dependent on Bcl-2 for survival; therefore a risk for hair colour change in CLL patients cannot be excluded (see also discussion on clinical safety).

Venetoclax was tested negative in a complete package of genotoxicity studies including test for gene mutations and chromosomal aberrations *in vitro* and chromosomal aberrations *in vivo*. No carcinogenicity studies were performed which in view of the applied indication is acceptable according to ICH S9.

In fertility and early embryonic development studies conducted in male and female mice there were no treatment-related effects on any of the investigated parameters. However, in dogs, venetoclax caused irreversible testicular germ cell depletions at exposures below the clinical exposure, suggesting a risk for irreversible infertility in male patients treated with venetoclax. The testicular germ cell depletions in dogs may be related to venetoclax pharmacology, as one or more members of the Bcl-2 family of proteins play a role in spermatogenesis. However, no testicular changes were evident in mice, and the basis for the greater sensitivity of dogs as compared with that of mice to testicular germ cell decreases is unclear. Based on the severe testicular toxicity in dogs, section 4.6 of the SmPC includes a recommendation that counselling on sperm storage may be considered in male patients prior to

initiation of treatment. Testicular toxicity is considered a potential risk for the human situation, and is also included as such in the RMP.

Embryo-foetal development toxicology studies were conducted in pregnant mice and rabbits. In the rabbit study, 4 dams were found dead or euthanized at the highest dose tested, 300 mg/kg/day. These early deaths were preceded by adverse clinical signs, maternal body weight losses and severely reduced food consumption and necropsy revealed gross abnormalities in the GI tract in three out of the four dams. The mean AUC at 300 mg/kg/day on GD19 was 4900 ng·h/mL corresponding to ~0.2 fold the clinical AUC. Therefore, the rabbit seems more sensitive to venetoclax-related effects than the other investigated species.

Regarding embryo-foetal effects, no venetoclax-related malformations indicative of a teratogenic potential were observed in the performed mouse and rabbit EFD studies. However, the results of the preliminary mouse study show serious embryo-foetal toxicity, i.e. a dose-related increased post-implantation loss up to about 90% at the highest dose corresponding to about 2 times clinical exposure and in the absence of overt maternal toxicity. No embryo-foetal toxicity was observed in the rabbit studies, but as the exposures were about 0.1-fold the clinical exposure, the lack of embryo-foetal toxicity is not considered reassuring for the human situation. Nevertheless, the limited data available from the mouse EFD studies indicate serious concern for use during pregnancy. In addition, as venetoclax is first-in-class, clinical experience is lacking. Therefore, embryo-foetal toxicity is included as an important potential risk in the RMP.

The results of an *in vivo* phototoxicity study in mice suggest that venetoclax has a low phototoxic potential.

Metabolite 27, a major human metabolite, was tested negative in *in vitro* genotoxicity studies. M27 was present in both mice and dogs at the maximum tolerated dose, but at much lower exposures than in humans. Although M27 cannot be considered as qualified from a non-clinical perspective, further non-clinical testing is not warranted based on the intended target population with advanced cancer.

Environmental risk assessment

Venetoclax is considered not to be PBT, nor vPvB. A risk to the STP is not anticipated based on the prescribed use of venetoclax. Correction of the PEC calculation in the environmental risk assessment should be provided in accordance with the ERA guideline.

2.3.7. Conclusion on the non-clinical aspects

The pharmacology, safety pharmacology, pharmacokinetics and toxicology programs are considered sufficient.

All relevant information has been included in sections 4.6 and 5.3 of the SmPC. The risk of embryo-foetal toxicity is included as a potential important risk in the RMP.

Correction of the PEC calculation in the environmental risk assessment should be provided.

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points to be addressed

- To correct the PEC calculation in the environmental risk assessment in accordance with EMA guidance.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 11: Studies Supporting the Efficacy and Safety of Venetoclax in CLL for the CMA.

Protocol	Phase	Study Design	Subjects All/17p del	Median Treatment Duration
Efficacy and Safety				
M13-982 (Pivotal study)	2	Open-label, multicenter, study evaluating the efficacy of venetoclax in R/R or previously untreated subjects with CLL harboring 17p del.	107/106[a]	12.1 months
M12-175 Arm A	1	First-in-human, open-label, dose-escalating, multicenter study evaluating the safety and PK of venetoclax in subjects with R/R CLL/SLL	67/31[b]	13.0 months
M14-032	2	Open-label, nonrandomized, multicenter study evaluating the efficacy and safety of venetoclax in subjects with R/R CLL after failure of a BCRi	28/9	2.3 months
M13-365[c]	1b	Open-label, dose-escalating, multicenter study evaluating the safety and tolerability of venetoclax in combination with rituximab in subjects with relapsed CLL/SLL.	49/9	13.3 months
Safety Only				
M12-175 Arm B	1	Open-label, food effect study of venetoclax monotherapy in subjects with R/R NHL (Arm B)	106	
GO28840[d,e]	1b	Open-label, dose-escalation study of venetoclax in combination with BR in subjects with R/R or previously untreated CLL	19	
GP28331[d,e]	1b	Open-label, dose-finding and safety study of venetoclax in combination with obinutuzumab in subjects with R/R or previously untreated CLL	20	

Protocol	Phase	Study Design	Subjects All/17p del	Median Treatment Duration
Clinical Pharmacology				
M14-253	1	Open-label, 2-period, randomized, crossover study of the bioavailability of venetoclax in healthy female subjects of non-childbearing potential	15	
M14-497	1	Open-label study to assess the effect of rifampin on the PK of venetoclax in healthy female subjects of non-childbearing potential	12	
M13-363	1	Open-label, ADME study in healthy female subjects of non-childbearing potential	4	
M13-364	1	Open-label, study to assess effect of ketoconazole on the PK of venetoclax in subject with R/R NHL	12	
M15-065	1	Open-label study to assess the effect of venetoclax on the PK of warfarin in healthy female subjects of non-childbearing potential	8	
M15-101	1	Open-label, randomized, 4-period, complete, crossover study of the bioavailability and food effect of venetoclax in healthy female subjects of non-childbearing potential	24	

2.4.2. Pharmacokinetics

Pharmacokinetic data are available from six efficacy and/or safety studies in patients with CLL/SLL or NHL and from six dedicated biopharmaceutic/pharmacokinetic studies in NHL patients or in healthy female volunteers of non-childbearing potential, including drug-drug interaction studies.

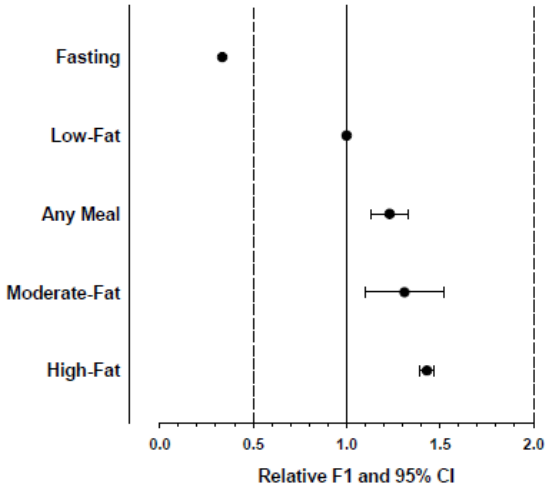
Biopharmaceutics and absorption

Venetoclax is considered practically insoluble or insoluble (≥ 10,000 parts of solvent to dissolve 1 part of solute) in aqueous solutions across a pH range of 1 to 12.9. The solubility in aqueous buffer is pH-dependent.

The commercial formulation is an immediate-release film-coated tablet, available in the strengths 10 mg, 50 mg and 100 mg. Comparable bioavailability has been shown between clinical trial formulations and the market formulation. There is no bioavailability comparison between different strengths.

A study in Caco-2 cells indicated that venetoclax may have moderate permeability, and would therefore be classified as a Biopharmaceutics Classification System (BCS) class IV compound. However, the Caco-2 cell study was inconclusive. In the mass-balance study, the degree of absorption from an oral solution appeared to be high (>85%) at administration with food. The absolute bioavailability is not known. Based on a clinical interaction study, there is likely some first-pass metabolism via CYP3A4.

Figure 4: Forest plot of the food effect in the population pharmacokinetic model



After administration of the film-coated tablet with food (generally within 30 minutes after breakfast), Tmax values of about 4-8 hr have been observed in different studies. The Tmax in the mass-balance study (oral solution with food) was in the same range.

No effect of gastric acid-reducing agents on venetoclax exposure was seen in a population pharmacokinetic analysis, but the results should be interpreted with caution as short- and long-acting agents were grouped together and the exact dosing information for the short-acting agents was not known/reported.

The effect of alcohol on the disintegration, dissolution and solubility of venetoclax 10 and 100 mg tablets was investigated. The effects of ethanol appeared to be dose dependent with more pronounced effects for the 100 mg tablet. Ethanol accelerated the disintegration of venetoclax 100 mg tablets but data suggest that in presence of 20% and 40% ethanol, the solubility of venetoclax in the dissolution medium is lower and drug release is incomplete.

Distribution

The mean estimated V2/F in the population pharmacokinetic analysis was 118 L.

Venetoclax and M27 are highly protein bind in human plasma. The mean unbound fraction (fu) of venetoclax was 0.000013. There was no concentration dependence (1-30 µM). For M27, the unbound concentrations were below the limit of quantitation (1 nM) of the HPLC-MS/MS analytical method in most samples. The calculated unbound fraction of M27 was <0.0028 in human plasma. The mean unbound fraction of venetoclax in human liver microsomes (0.25 mg/mL) was around 0.0012 µM. The unbound fraction of venetoclax in 4% bovine serum albumin (BSA) could not be determined because it was below the limit of detection.

Blood-plasma ratios of venetoclax and M27 in human blood were 0.57 and 0.47, respectively.

Elimination

All studies on elimination and drug-drug interactions have been performed in the fed state.

Mass-balance data indicate that absorption of venetoclax is complete or almost complete after administration of *an oral solution* with a moderate-fat breakfast, as most of the recovered drug-related

material was found in late faecal samples. Excretion of venetoclax and metabolites was almost exclusively in faeces. Urinary excretion was minimal (<0.1% of the dose). About 80% of the dose was recovered as metabolites in faeces, and 20% as venetoclax. Metabolism appears to be the major elimination pathway, but there is some uncertainty whether the major metabolites in faeces were formed locally in the intestine from venetoclax that had been excreted unchanged. If this is the case, excretion of unchanged parent may represent up to about 50% of the elimination.

Over 30 different metabolites have been identified. The only major metabolite in plasma, M27, has an $AUC_{0-\infty}$ that is 40-50% of parent $AUC_{0-\infty}$ after repeated doses. M27 is considered minimally active against Bcl-2 and is not expected to contribute to the overall pharmacological activity. No other metabolites accounted for more than 10% of the radioactivity in plasma.

In vitro, venetoclax and M27 were metabolised primarily via CYP3A4. There was no involvement of UGTs or FMO3. The importance of CYP3A4-mediated metabolism was confirmed by an *in vivo* interaction study with the CYP3A4/Pgp inhibitor ketoconazole.

Both venetoclax and M27 are substrates of Pgp and BCRP, and these transporters may therefore be involved in the absorption and first-pass metabolism as well as the excretion of unchanged venetoclax. Venetoclax is likely not an OATP1B1/1B3 substrate.

Apparent clearance (CL/F) estimated in the population analysis was 447 L/Day (18 L/hr). The population estimate for the terminal elimination half-life of venetoclax was approximately 26 hours. This is in line with the half-life determined in the single dose mass-balance study, which was 23 hr. Metabolite M27 had a half-life of approximately 59 hr in the mass-balance study.

Dose linearity and time dependency

In a dose-escalation study and in the population pharmacokinetic analysis, there was a slight tendency to decreased dose-normalised AUC with increasing doses over the dose range 20-1200 mg. There was no sign of altered pharmacokinetics over time at multiple dosing. Based on the population pharmacokinetic analysis, the accumulation of venetoclax with daily dosing in male and female cancer patients was 1.44 and 1.30, respectively.

Variability

As often seen for CYP3A4 substrates, venetoclax pharmacokinetic inter-individual variability is high with a total variability coefficient of variation (%CV) in C_{max} and AUC of approximately 50% at the 400 mg dose at steady-state. In the population pharmacokinetic analysis, the %CV of the inter-individual variability for CL/F, V2/F, and F1 were 47.7%, 58.0%, and 31.3%, respectively.

Target population

Pharmacokinetics of venetoclax was described by a two-compartment PK model with first-order absorption and elimination. The population pharmacokinetic analysis predicted no difference in venetoclax CL/F between healthy subjects and patients with CLL/SLL or NHL, respectively. CLL/SLL/NHL subjects were estimated to have V2/F that is 1.71-fold higher than healthy subjects. This difference was likely caused by the more frequent sampling in studies in healthy subjects and better capturing Cmax. The difference in V/F does not affect exposure (AUC).

Special populations

The effects of different intrinsic factors on venetoclax pharmacokinetics have been evaluated by population pharmacokinetic analysis of sparse and/or rich data from eight phase 1/1b/2 clinical studies.

There was no effect of mild to moderate renal impairment on venetoclax clearance, which was expected based on the minimal renal excretion of venetoclax observed in the mass-balance study. Data for severe renal impairment and ESRD is missing.

There was no effect of mild hepatic impairment on venetoclax CL/F. The population pharmacokinetic analysis included only 7 and one patient with moderate and severe hepatic impairment, respectively, and no conclusions can be drawn for these populations. A study in severe hepatic impairment is planned.

CLL is primarily a disease of adults, particularly the elderly. Venetoclax exposure was not different in elderly patients compared to younger patients. The population pharmacokinetic analysis also indicated no relevant effects of sex, age or weight on venetoclax CL/F. The evaluation of potential effects of race is hampered by the very limited number of patients of other races than Caucasian and Black that were included in the analysis.

There is no pharmacokinetic data in children, which is acceptable given the indication applied for.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	2/70	5/70	0/70

Pharmacokinetic interaction studies

Venetoclax as victim

In vitro data showed that venetoclax is a substrate for CYP3A4, Pgp and BCRP. Accordingly, *in vivo* interaction studies have been performed with a CYP3A4/Pgp inhibitor (ketoconazole) a PXR inducer (multiple dose rifampicin) and a Pgp inhibitor (single dose rifampicin).

Ketoconazole increased venetoclax AUC by on average 6.4-fold, with large inter-individual variability in the effect. Also Cmax and half-life increased, indicating an effect on first-pass metabolism as well as on elimination. AUC for the metabolite M27 decreased upon ketoconazole co-treatment, in line with decreased formation. Multiple-dose rifampicin decreased venetoclax AUC by 70%. These data confirm the contribution of CYP3A4/Pgp to the elimination of venetoclax.

Single-dose rifampicin led to about 80% increase in the AUC of venetoclax, which may be due to inhibition of Pgp.

Venetoclax and M27 as perpetrators

The potential of venetoclax and M27 to inhibit or induce CYPs and to inhibit UGTs or transporters has been primarily investigated *in vitro*. There is one *in vivo* interaction study with warfarin (CYP2C9 substrate).

Based on the IC50s determined in the *in vitro* studies and comparison with the clinical exposure data, venetoclax and, in some cases, M27 may be clinically relevant competitive inhibitors of CYP2C8, CYP2C9, UGT1A1, Pgp, BCRP and OATP1B1. There were no signs of time-dependent inhibition *in vitro*. No potential to inhibit *systemic* CYP3A4 was seen, while the concentrations in the *in vitro* studies were too low to determine the risk for inhibition (competitive or time-dependent) of *intestinal* CYP3A4 by venetoclax.

In vitro induction data were inconclusive due to cell toxicity at higher concentrations. There was a small signal of induction of CYP1A2 and 2B6 (i.e. induction via Ah receptor and CAR) for venetoclax.

There was no sign of induction of CYP3A4 (i.e. induction via PXR) at relevant systemic or attainable gut concentrations, taking the low solubility of venetoclax in intestinal fluid into account.

The most sensitive CYP for *in vitro* inhibition by venetoclax was CYP2C9. An *in vivo* interaction study with the narrow-therapeutic index substrate warfarin was performed in healthy female volunteers of non-childbearing potential. Only a single dose of venetoclax was administered, and the effect is likely underestimated. The AUC of S-warfarin (CYP2C9 substrate) increased about 28% and AUC of R-warfarin (CYP3A4 substrate) increased about 20%. As an effect was seen on both R-warfarin, which is not a CYP2C9 substrate, and S-warfarin it was suggested that the effect was not a result of CYP2C9 inhibition.

PBPK modelling

A PBPK model was used to simulate effect of different moderate and severe CYP3A4 inhibitors on venetoclax exposure, in order to support proposed dosing recommendations for venetoclax if CYP3A4 inhibitors need to be concomitantly administered.

The effects of different moderate and strong CYP3A inhibitors were evaluated, in order to take into account differences of potency. The moderate CYP3A inhibitors were estimated to increase the venetoclax C_{max} by 1.40- to 2.00-fold and increase the venetoclax AUC_{∞} by 1.98- to 4.85-fold. Thus, for all the evaluated moderate inhibitors the venetoclax AUC_{∞} increased by at least 2-fold, which is the recommended minimal venetoclax dose reduction with moderate CYP3A inhibitors. The strong CYP3A inhibitors were estimated to increase the venetoclax C_{max} by 2.02- to 2.50-fold and increase the venetoclax AUC_{∞} by 5.82- to 7.83-fold. In all cases, the recommend 4-fold reduction in venetoclax dose with strong CYP3A inhibitors maintains the AUC_{∞} above the equivalent AUC_{∞} that would be achieved in the absence of a strong CYP3A inhibitor at 400 mg.

Inter-individual variability in venetoclax exposure was similar with and without CYP3A4 inhibition. Simulations of individual venetoclax exposures obtained when using the proposed dose reductions with different CYP3A4 inhibitors was performed. These simulations indicated that the recommended dose reductions with moderate and strong CYP3A inhibitors generally maintains the venetoclax AUC_{24} exposures within the range achieved at 400 mg QD and 1200 mg QD. With erythromycin, the simulated median venetoclax AUC_{24} achieved with 200 mg venetoclax was above that achieved 1200 mg QD alone, but there was considerable overlap between the individual exposures.

2.4.3. Pharmacodynamics

Mechanism of action

The mechanism of action was investigated in non-clinical studies.

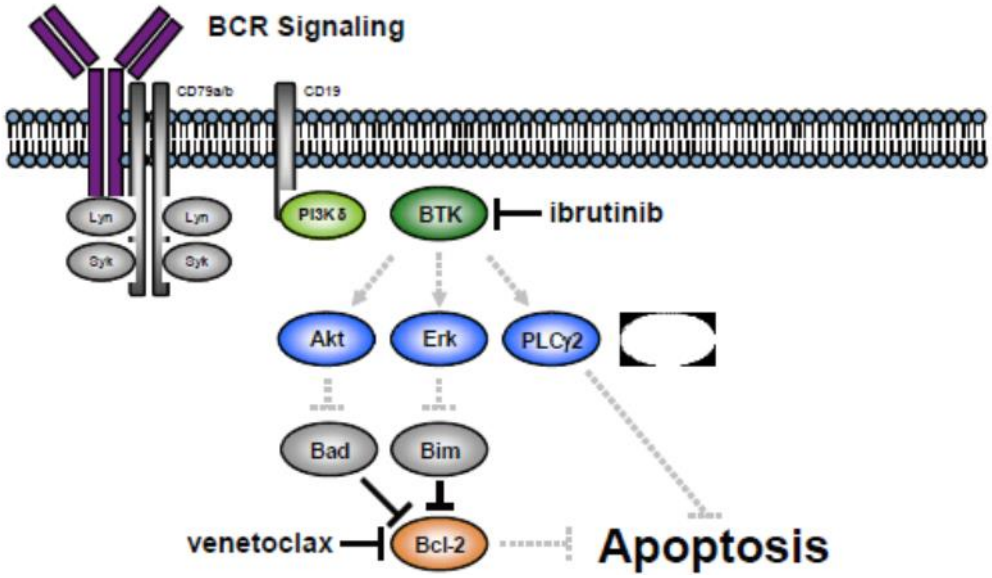
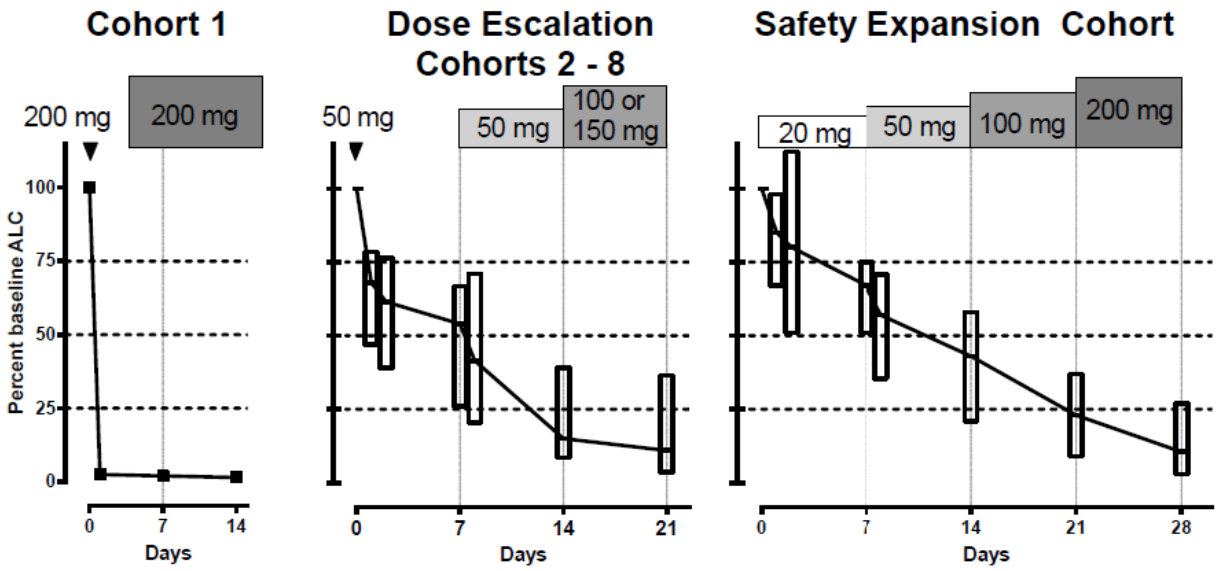


Figure 5: Targeting BCR signalling in CLL including Venetoclax (ABT-199).

Primary and Secondary pharmacology

In study M12-175 116 subjects with relapsed or refractory CLL or SLL were treated with venetoclax: 56 subjects across 8 dose escalation cohorts (150 mg to 1200 mg) and in 60 subjects in the 400 mg safety expansion cohort. For CLL/SLL subjects, the initial dose was 200 mg per the original protocol and then was decreased to ≤ 50 mg and finally to 20 mg for TLS prophylaxis.

Mean and median time to 50% reduction in lymphocyte count among subjects with baseline lymphocyte count > 5 × 10^9/L was 1.9 and 2.0 weeks, respectively, for subjects in the dose escalation cohorts and 1.6 and 1.3 weeks, respectively, for subjects in the safety expansion cohort. Among subjects with lymphocytosis (ALC > 5 × 10^9/L) at baseline, ALC decreased in a dose-dependent manner after the first dose by a median of 15%, 33% and 97% for 20 mg, 50 mg, and 100/200 mg first doses, respectively (see Figure 6). There was a more gradual reduction in ALC following the initial cohort and implementation of the extended titration period.



ALC = absolute lymphocyte count; DE = dose escalation; SE = safety expansion

Notes: Cohort 1: baseline (immediately prior to first dose), Day 1 (24 hours after first dose), Day 7 (Week 1 Day 1), and Day 14 (Week 2 Day 1). DE and SE Cohorts: baseline (immediately prior to first dose), Day 1 (24 hours after first dose), Day 2 (48 hours after first dose), Day 7 (Week 1 Day 1), Day 8 (24 hours after second dose), Day 14 (Week 2 Day 1), and Day 21 (Week 3 Day 1).

Only data from subjects with lymphocytosis (ALC > 5×10^9/L) at baseline are included in the analysis: 100 – 200 mg (cohort 1, n = 2) or 50 mg (DE cohorts 2 – 8, n = 27) or 20 mg (SE cohort, n = 35).

ALC data are normalized to the ALC immediately prior to dosing, and plots represent median and 10^{th} – 90^{th} percentiles.

Cohort 1 included 3 subjects. Subjects 101 and 103 received 200 mg as an initial dose and Subject 104 received a 100 mg initial dose.

Figure 6 Percent change in lymphocyte count from baseline during the titration period – CLL/SLL Subjects (study M12-175).

High response rates were observed across the dose cohorts and subpopulations (see Table 12). Initial responses were observed early with 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.

Table 12: Summary of Response – CLL/SLL Subjects in dose escalating cohorts (M12-175).

	<400 mg N=22	400 mg N=7	>400 mg N=27
ORR	14 (63.6%)	6 (85.7%)	23 (85.2%)
CR+Cri	3 (13.6%)	2 (28.6%)	12 (44.4%)
DOR 6 month 12 month	N=14 85.7% 63.5%		N=23 100% 90.9%

Analysis of preliminary efficacy, pharmacokinetics, and overall safety in Study M12 -175 at doses from 150 to 1200 mg venetoclax for CLL/SLL subjects led to the selection of 400 mg as the dose to explore further in the CLL/SLL safety expansion cohort of this study. At the time of the dose selection, time on study was limited to the first 6 to 12 months, with shorter follow-up for the higher dose cohorts. ORR was not different when comparing results for subjects treated at 400 mg versus those treated at higher doses. No maximum tolerated dose was established, but adverse events were slightly higher at doses higher than 400 mg. The 400 mg QD dose was selected to obtain additional safety information at that dose level.

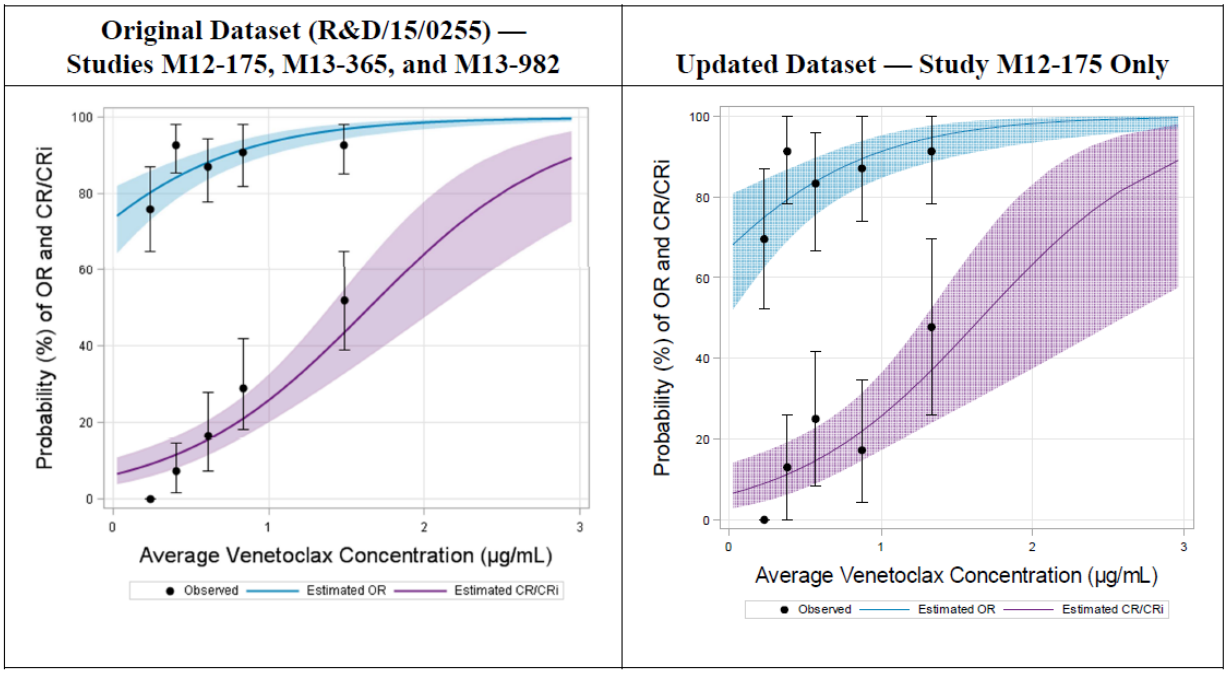
Dose response was also evaluated for venetoclax when administered in combination with rituximab. Study M13-365 was a Phase 1b, open-label, non-fasting, multicenter study designed to evaluate the safety and tolerability of venetoclax in combination with rituximab in subjects with relapsed CLL/SLL. After the lead-in period (Weeks 1 through 5), subjects within each cohort received venetoclax 200, 300, 400, 500 or 600 mg QD in combination with rituximab. The study is ongoing. Preliminary activity of venetoclax in combination with rituximab demonstrated that the majority of subjects (40 [81.6%]) across all cohorts achieved objective response (13 CR, 5 CRi, 2 nPR, and 20 PR). Efficacy was observed at all doses (see Clinical efficacy)

Exposure response relationship

The exposure-effect and exposure-safety relationship for venetoclax have been evaluated by a population PKPD analysis and by repeated measures logistic regression analysis.

Efficacy data (i.e., lymphocytes, tumour size, and OR/CRi/CR) from three Phase 1 and Phase 2 clinical trials of venetoclax monotherapy or combination therapy (with rituximab) in R/R CLL/SLL subjects were included in the exposure-efficacy analysis. 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%. The model also indicated that decreasing the dose to 200 mg would not relevantly affect response rate.

Figure 7: Probability of achieving OR and CR/Cri versus average venetoclax concentration: orginal versus updated



A repeated measures logistic regression analysis between exposure and objective response in CLL/SLL was conducted at the time of Phase 2 dose selection. This analysis predicted a difference in ORR between the 400 mg and 600 mg doses at early time points; however, the difference was negligible after 24 weeks of treatment. Contrary to the exposure-effect model, the regression analysis led to the conclusion that a dose of 200 mg may be somewhat less effective than 400 mg.

The exposure-safety relationship was evaluated for infection and neutropenia. Logistic regression analyses of the adverse events (Grade ≥ 3) of neutropenia and infection indicated that higher average venetoclax concentrations were associated with a decreased probability of the adverse event. It is hypothesised that the effect is driven by improving disease treatment. Therefore, the safety endpoints of ≥ Grade 3 neutropenia and infection are not dose limiting.

In dose-response studies, a MTD was not defined (doses up to 1200 mg), but data suggested an increase in adverse events at doses higher than 400 mg, although it was not dose-limiting. The risk for tumour lysis syndrome during the titration phase has been observed to be increased at increased doses/exposure.

Exposure QT Response Analyses

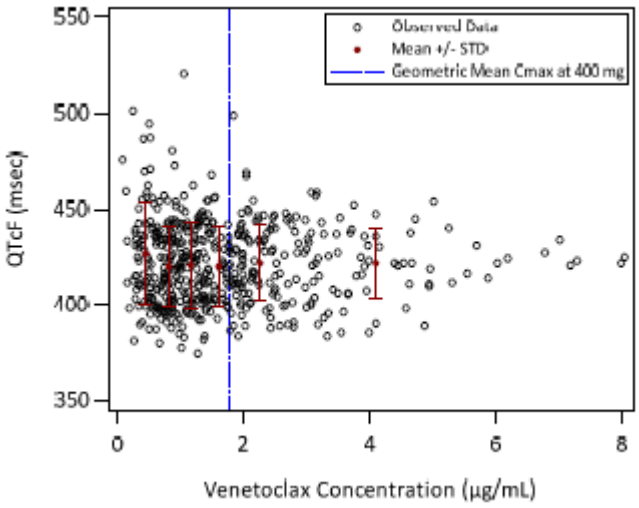
The central tendency, categorical and exposure-response analyses components of this QT/QTc assessment were determined in Study M12-175 (R&D/15/0254) where electrocardiogram (ECG) measurements were collected in triplicate at multiple time-matched points (2, 4, 6 and 8 hours) at baseline (prior to the first dose administration) and at steady state (at 3, 6 or 7 weeks of dose administration) in subjects with R/R CLL and NHL. Steady-state doses of venetoclax in this study ranged from 100 to 1200 mg QD. Blood samples for plasma venetoclax assay were collected after each steady-state time-matched triplicate ECG collection.

A total of 176 subjects had at least one QTcF measurement at baseline or steady state, while 147 subjects had at least one steady-state QTcF measurement. Of the 518 steady-state QTcF

measurements from 147 subjects, 84.3% (437 out of 518), 9.7% (50 out of 518), and 6.0% (31 out of 518) of the QTcF measurements were from the average of triplicate, duplicate, and single readings, respectively.

Plotting of the QTcF versus venetoclax concentrations indicated no relationship over the range of concentrations observed up to the 1200 mg QD dose.

Figure 8: QTcF Versus Venetoclax Plasma Concentrations (Observed)



2.4.4. Discussion on clinical pharmacology

Venetoclax is very lipophilic and practically insoluble in aqueous solutions. Venetoclax tablets are formulated to enable adequate in vivo absorption. Although absolute bioavailability has not been determined, the absorption of venetoclax under normal conditions is considered sufficiently well-established through biopharmaceutic and mass-balance studies.

Absorption of venetoclax under fasting conditions is low. Food increased bioavailability by 3- to 5-fold depending on fat content. Venetoclax has been administered with food in all clinical efficacy/safety studies. Administration with a low-fat meal may be considered the standard condition based on the recommendation given in the efficacy and safety studies to take venetoclax with breakfast. The 40-50% higher exposure with a high-fat meal as compared with a low-fat meal is likely not clinically relevant, and it is therefore acceptable not to define the fat content of the concomitant meal in the SmPC.

Venetoclax has pH dependent solubility, with somewhat higher solubility at pH 1 and 12, and lower solubility at pH 4 and 7. However, the solubility is still extremely low over the whole pH range. Given that venetoclax is to be administered with food, i.e. at a state with somewhat increased gastric pH and where solubilising agents in the food and gastric fluids likely increases bioavailability, acid-reducing agents are not expected to affect venetoclax bioavailability.

The elimination of venetoclax is sufficiently well characterised. Venetoclax is almost exclusively hepatically eliminated. Based on the elimination mechanisms (CYP3A4 metabolism, transport via Pgp and BCRP), the relevant *in vivo* interaction studies have been performed, i.e. with ketoconazole (CYP3A4/Pgp inhibitor) and rifampicin (PXR inducer and Pgp inhibitor).

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

increased venetoclax C_{max} by 106% and AUC_{∞} by 78%. A Pgp inhibitor increased venetoclax AUC by about 80%. It is therefore recommended to avoid Pgp and BCRP inhibitors during the titration phase. During the maintenance phase, patients should be monitored more closely for signs of toxicity.

A single, major plasma metabolite, M27 was identified. As M27 does not contribute to the pharmacological activity of venetoclax, its elimination or its potential to be affected by drug-drug interactions as a victim do not need to be thoroughly investigated.

Co-administration of 400 mg once daily ketoconazole, a strong CYP3A, P-gp and BCRP inhibitor, for 7 days in 11 patients increased venetoclax C_{max} by 2.3-fold and AUC_{∞} by 6.4-fold. Co-administration of venetoclax with other strong CYP3A4 inhibitors is predicted to increase venetoclax AUC by on average 5.8- to 7.8-fold. (see SmPC section 4.5). As venetoclax has a long half-life, administration of ketoconazole on a BID schedule is predicted to give a larger effect.

The use of strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, clarithromycin, itraconazole, voriconazole, posaconazole) during the titration phase is contraindicated in the SmPC, (see section SmPC 4.3 and 4.5) due to the risk for TLS. When titration is completed, an at least 4-fold dose reduction with strong CYP3A4 inhibitors, and a 2-fold reduction with moderate inhibitors is possible. In order to demonstrate that the proposed dose recommendations will maintain adequate venetoclax exposure for CYP3A4 inhibitors of different potency, PBPK simulations were performed. The results of these simulations indicate that the proposed 2-fold dose reduction at concomitant administration of moderate CYP3A4 inhibitors and 4-fold reduction with strong CYP3A4 inhibitors will not lead to under-exposure of venetoclax in comparison with the exposure at 400 mg without inhibition, and will not lead to higher exposure than with the 1200 mg dose administered in the multiple-dose ascending dose study. The PBPK model appeared to adequately describe venetoclax pharmacokinetics, and the observed effect of ketoconazole 400 mg daily was well predicted. The effect of a 200 mg BID dosing of ketoconazole was estimated to be a 7.8-fold increase in venetoclax AUC, in line BID ketoconazole this being a worst case for a victim with a long half-life.

Grapefruit products, Seville oranges, and starfruit (carambola) should be avoided during treatment with venetoclax as they contain inhibitors of CYP3A (see SmPC section 4.5).

The potential of venetoclax and its major metabolite M27 to act as perpetrators in drug-drug interactions was thoroughly investigated *in vitro* in accordance with the EMA interaction guideline. The *in vitro* evaluation was in general sufficient, except that *in vitro* induction data for CYP1A2 and CYP2B6 are considered inconclusive, and new *in vitro* studies will be performed as PAMs (see RMP).

Venetoclax was identified as an inhibitor of the enzymes CYP2C8, CYP2C9, and UGT1A1. M27 inhibited CYP2C9 and UGT1A1. An *in vivo* interaction study with warfarin, however, demonstrated a very small effect on S- and R-warfarin, and the effect is considered unlikely to be mediated by CYP2C9 inhibition as also R-warfarin was affected, which suggests it may be an effect on Pgp. For most substrates, the observed increase in AUC would not be considered clinically relevant but it is agreed that a warning of INR monitoring should be given if warfarin is co-administered with venetoclax. Overall it is accepted that venetoclax is unlikely to cause clinically relevant increases in the exposure of CYP2C9 substrates. As IC50 values for CYP2C8 and UGT1A1 were in the same range as for CYP2C9, relevant *in vivo* inhibition of these enzymes would also not be expected.

Venetoclax was identified as an inhibitor of P-gp and BCRP. Both venetoclax and M27 inhibited OATP1B1. Caution is recommended at concomitant treatment with substrates of these transporters e.g. anti-coagulants. For narrow-therapeutic index substrates of P-gp or BCRP that are sensitive to inhibition in the gastrointestinal tract (dabigatran is presently the most well-known example), dosing should be staggered in relation to venetoclax administration (see SmPC section 4.5.). Several anti-

coagulants used such as dabigatran, rivaroxaban are substrates for P-glycoprotein and, thus, venetoclax may increase their exposure (see discussion on clinical safety). If a statin (OATP substrate) is used concomitantly with venetoclax, close monitoring of statin-related toxicity is recommended.

Co-administration of 600 mg once daily rifampin, a strong CYP3A inducer, for 13 days in 10 healthy subjects decreased venetoclax C_{max} by 42% and AUC_{∞} by 71%. Concomitant use of Venetoclax with strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin) or moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) should be avoided. Alternative treatments with less CYP3A induction should be considered. Preparations containing St John's wort are contraindicated during treatment with venetoclax, as efficacy may be reduced (see section 4.3).

Based on population pharmacokinetic analysis, gastric acid reducing agents (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) do not affect venetoclax bioavailability (see SmPC section 4.5). Co-administration of bile acid sequestrants with venetoclax is not recommended as this may reduce the absorption of venetoclax. If a bile acid sequestrant is to be co-administered with venetoclax, the SmPC for the bile acid sequestrant should be followed to reduce the risk for an interaction, and venetoclax should be administered at least 4-6 hours after the sequestrant.

In a drug-drug interaction study in three healthy volunteers, administration of a single dose of 400 mg venetoclax with 5 mg warfarin resulted in an 18% to 28% increase in C_{max} and AUC_{∞} of R-warfarin and S-warfarin. Because venetoclax was not dosed to steady state, it is recommended that the international normalized ratio (INR) be monitored closely in patients receiving warfarin (see SmPC section 4.5).

The effect of different intrinsic and some extrinsic factors on venetoclax pharmacokinetics was evaluated by population pharmacokinetic analysis. The population pharmacokinetic model appeared to perform adequately, although the evaluation of some co-variate effects was hampered by limitations in the dataset, as further discussed below. There was no effect of mild to moderate renal impairment on venetoclax clearance, as expected based on the minimal renal excretion of venetoclax. As severe renal impairment might impact elimination of hepatically eliminated drugs and given the increased TLS risk at renal impairment, the SmPC advices that venetoclax should be administered to patients with severe renal impairment only if the potential benefit outweighs the risk, and that patients should be more closely monitored for toxicity.

There was no effect of mild hepatic impairment on venetoclax CL/F. The population pharmacokinetic analysis included only 7 and one patient with moderate and severe hepatic impairment, respectively, and no conclusions can be drawn for these populations. As Venetoclax is hepatically eliminated an increased exposure could be expected in patients with metabolic impairment of the liver. A study in hepatic impairment is planned; the SmPC recommends close monitoring of patients with moderate impairment, while venetoclax treatment is not recommended for patients with severe hepatic impairment, given the risk of significantly increased exposure and thereby increased risk of TLS.

Based on non-clinical data in mice, venetoclax is not classified as a teratogen, but showed clear embryo-foetal toxicity. Due to maternal toxicity there were no exposure margins to clinical exposure in these studies and it cannot be completely excluded that venetoclax is a human teratogen at higher exposures. The SmPC (section 4.6.) recommends that female patients of childbearing potential should avoid pregnancy and further advices that as it is currently unknown whether venetoclax may reduce the effectiveness of hormonal contraceptives, women using hormonal contraceptives should add a barrier method. Furthermore, an *in vivo* interaction study with an oral contraceptive will be performed post-authorisation (see RMP).

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics and the interaction potential of venetoclax and its major metabolite M27 have been thoroughly investigated and all available information has been included in the SmPC sections 4.5 and 5.2.

Additional *in vitro* and *in vivo* interaction data including *in vitro* induction data on CYP1A2 and CYP2B6 and a drug-interaction study on the effect of venetoclax on the pharmacokinetics of oral contraceptives will be provided as part of post-approval measures (see RMP).

The clinical pharmacology data have been adequately reflected in the SmPC sections 5.2, 4.5 and 4.6.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

Study M12-175

Dose response study

Protocol M12-175: A Phase 1 Study Evaluating the Safety and Pharmacokinetics of ABT-199 in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukaemia and Non-Hodgkin Lymphoma (Interim Clinical Study Report)

This was a multicenter study conducted in Australia, Canada, France, Germany, Poland, United Kingdom, and United States of America (USA). A total of 56 investigative sites were approved to receive study drug supplies on behalf of the Sponsor, AbbVie Inc. (AbbVie), and screen and enroll subjects in the study. As of the data cutoff date of this interim clinical study report subjects were enrolled at 38 investigative sites.

Methods

- **Study participants**

Inclusion Criteria

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

1. Signed informed consent
2. Subject was ≥18 years of age
3. diagnosis of CLL that met published 2008 Modified Guidelines from the International Workshop for Chronic Lymphocytic Leukaemia (IWCLL) NCI WG

- Subject had an indication for treatment according to the 2008 Modified Guidelines from the International Workshop for Chronic Lymphocytic Leukaemia (IWCLL) NCI WG
- Subject had clinically measurable disease defined in Protocol Amendment 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 (Protocol Amendments 1 through 3) or previously untreated CLL (Protocol Amendment 3 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 [Protocol Amendments 2 and 3, safety expansion cohort] or had completed at least 2 cycles of treatment for a given line of therapy [Protocol Amendment 1]
    - 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 (e g for relief of compressive signs or symptoms) were eligible
        - CLL diagnostic criteria above and subjects had to have >5 × 10^9 cells/ L B lymphocytes in the peripheral blood
- Subject had the17p deletion assessed by
    - Protocol Amendment 1 (main cohort): central laboratory (peripheral blood), and determined by FISH using the Vysis CLL probe kit
    - Starting with Protocol Amendment 2 (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

4. Subject had an Eastern Cooperative Oncology Group (ECOG) performance score of ≤2
5. Subject had adequate bone marrow function at Screening as follows

- Absolute neutrophil count ANC ≥1000/µL or Protocol Amendment1 (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 be administered after Screening and prior to the first dose of venetoclax to achieve the ANC eligibility criteria ≥1000/µL. ; Starting with Protocol Amendment 2 (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) [redundant?], growth factor support could be administered after Screening and prior to the first dose of venetoclax to achieve the ANC eligibility criteria (≥1000/µL).
- Platelets; Protocol Amendment1 (main cohort): >40000/mm3 (entry platelet count had to be independent of transfusion within 14 days of Screening; Starting with Protocol Amendment 2 (safety expansion cohort) Platelets ≥30000/ mm3
- Haemoglobin ≥8.0 g/ dL

6. Subject had adequate coagulation renal and hepatic function per laboratory reference range at Screening as follows : Activated partial thromboplastin time (aPTT) and prothrombin time (PT) not to exceed 1.5 × the upper limit of normal (ULN); Calculated creatinine clearance >50 mL/ min using 24 hour creatinine clearance or modified Cockcroft Gault equation, estimated creatinine clearance rate using Cockcroft Gault formula [eCCr] using ideal body mass [IBM] instead of mass; 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 a bilirubin > 1.5 × ULN, per correspondence between the investigator and AbbVie medical monitor; 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

- Total abstinence from sexual intercourse ; Surgically sterile partner/s; acceptable sterility surgeries were: vasectomy, bilateral tubal ligation, bilateral oophorectomy, or hysterectomy; Intrauterine device; Double barrier method contraceptive sponge diaphragm or cervical cap with spermicidal jellies or cream AND a condom; Hormonal contraceptives oral parenteral or transdermal for at least months prior to study drug administration
- Females of childbearing potential i e not postmenopausal for at least year with no alternative medical reason or surgically sterile had negative results for pregnancy test performed at Screening with a serum sample obtained within 14 days prior to the first study drug administration; 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

Exclusion Criteria

A subject was not eligible for study participation if he she met any of the following criteria:

1. Subject had undergone an allogeneic stem cell transplant
2. Subject had developed Richter s transformation (confirmed by biopsy added starting with Protocol Amendment 2)
3. (Added starting with Protocol Amendment 2 for safety expansion cohort only): Subject had prolymphocytic leukaemia
4. 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)
- Starting with Protocol Amendment 2 (safety expansion cohort): for 2weeks prior to Screening, including AIHA and ITP despite low dose corticosteroids

5. Subject had previously received venetoclax
6. 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
7. Subject had received the following within weeks Protocol Amendment main cohort or within days starting with Protocol Amendment safety expansion cohort prior to the first dose of study drug

- A biologic agent (i e monoclonal antibodies) for anti-neoplastic intent

8. Subject had received any of the following within 14 days (Protocol Amendment 1, main cohort) or within 5 half-lives (Protocol Amendment 2, safety expansion cohort) or within 14 days or 5 half-lives (Protocol Amendment 3, safety expansion cohort), as applicable, prior to the first

dose of study drug or had not recovered to less than NCI CTCAE grade 2 clinically significant AEs of previous therapy.

9. Subject had received the following within days prior to the first dose of study drug

- Steroid therapy for anti-neoplastic intent
- Cytochrome P450 (CYP) 3A inhibitors such as fluconazole ketoconazole and clarithromycin
- Potent CYP3A inducers (eg rifampin, phenytoin, carbamazepine, or St John's Wort)
- 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
- (Protocol Amendment 1, main cohort only): antiretroviral medications
- Subject had consumed the following within 3 days prior to the first dose of study drug grapefruit or grapefruit products, seville oranges (including marmalade containing Seville oranges), star fruit

10. Subject had a known allergy to both xanthine oxidase inhibitors and rasburicase
11. 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
12. Subject exhibited evidence of other clinically significant uncontrolled condition s including but not limited to

- Protocol Amendment 1, main cohort: uncontrolled systemic infection (viral, bacterial, or fungal)
- Starting with Amendment 2,safety expansion cohort:
    - Uncontrolled and or active systemic infection (viral, bacterial, or fungal)
    - Chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) requiring treatment. Note: Subjects with serologic evidence of prior vaccination to HBV (i e hepatitis B surface antigen [HBsAg] negative, hepatitis B surface antibody [anti HBs] positive and hepatitis B core antibody [anti HBc] negative, and positive anti HBc from intravenous (IV) immune globulin could participate
    - Febrile neutropenia

13. Subject had a significant history of renal, pulmonary (starting with Protocol Amendment 2), neurologic, psychiatric, endocrine, 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 correspondence with the investigator and the AbbVie medical monitor had to occur
14. A female subject was pregnant or breastfeeding
15. Subject had a history of active malignancies other than CLL within the past 2 years prior to study entry with the exception of adequately treated in situ carcinoma of the cervix uteri basal cell carcinoma or localized squamous cell carcinoma of the skin previous malignancy confined and surgically resected (or treated with other modalities) with curative intent.
16. Subject had malabsorption syndrome or other condition that precluded enteral route of administration

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).

After the initial 3 CLL subjects in this study experienced laboratory TLS per Cairo Bishop definition laboratory 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 2-3 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.

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. This resulted in a Sponsor-initiated partial clinical hold for the venetoclax program.

In May 2013, the venetoclax clinical program was restarted under Amendment 8 (i.e., post-May 2013) 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. Amendment 9 implemented a 20 mg initial dose for CLL/SLL subjects for 1 full week.

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

Table 13: Venetoclax Dose Escalation in Study M12-175, Arm A (Subjects with CLL/SLL)

Cohort	Subjects Enrolled (N)	Venetoclax		
		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 (described in Section 9.1.1).

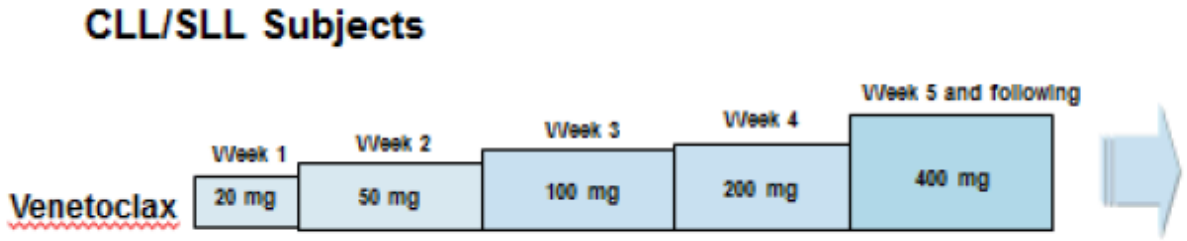
Note: Cohort 1 subjects were dosed at 100 mg and 200 mg venetoclax; there were no ramp-up doses.

A minimum of 3 subjects were enrolled per cohort. Escalation of venetoclax to the next designated cohort dose level in each arm was to proceed if all assigned subjects at a dose level completed the ramp-up period plus 3 weeks at the designated cohort dose without experiencing a DLT.

Safety Expansion Cohorts

Once the MTD/RPTD was declared, a cohort of approximately 60 additional CLL/SLL subjects in Arm A were to be enrolled in expanded safety portion. The dosing schedule for the expanded safety portion of the study (based on Amendment 10; post-May 2013) is depicted in the Figure below.

Figure 9: Dosing Schematic for Ramp-Up to Designated Cohort Dose – Safety Expansion Cohort – Arm A (CLL/SLL)



Results

Demographic and Baseline Characteristics

The CLL/SLL study subjects were heavily pre-treated with a mean of 3.5 prior therapies (range 1-10). Mean age was 64.8 years (range 25-86 y) and 97% had ECOG 0-1. A substantial proportion of subjects had CLL with risk factors for poor outcome (eg bulky disease ≥5 cm, fludarabine refractory, unmutated IGHV). Subjects were classified in 3 categories based on the risk for developing TLS as defined by tumour burden and ALC. TLS risk category was medium for or high for ~75%.

Certain CLL/SLL subjects in this study dose reduced based on events occurring in other subjects in the venetoclax program. Following 2 fatal events in the setting of TLS, all doses were reduced to 600 mg or less. Seven subjects in the 800 mg cohort were reduced to 600 mg and 2 subjects in the 1200 mg cohort received the cohort dose for 10 and 17 days only.

Table 14: Disposition of Subjects – CLL/SLL

	Number of Subjects (%)									
	Dose Escalation								Safety Expansion Cohort	
	Cohort 1 200 mg N = 3	Cohort 2 150 mg N = 6	Cohort 3 200 mg N = 6	Cohort 4 300 mg N = 7	Cohort 5 400 mg N = 7	Cohort 6 600 mg N =15[a]	Cohort 7 800 mg N = 7	Cohort 8 1200 mg[b] N = 5	400 mg N = 60	Total N = 116
Enrolled subjects	3	6	6	7	7	15	7	5	60	116
Treated subjects	3	6	6	7	7	15	7	5	60	116
Active at data cutoff (10 Feb 2015)	0	0	1 (16.7)	3 (42.9)	3 (42.9)	5 (33.3)	4 (57.1)	3 (60.0)	37 (61.7)	56 (48.3)
Discontinued	3 (100)	6 (100)	5 (83.3)	4 (57.1)	4 (57.1)	10 (66.7)	3 (42.9)	2 (40.0)	23 (38.3)	60 (51.7)
Primary reason for discontinuation:										
Adverse event	0	1 (16.7)	0	1 (14.3)	3 (42.9)	3 (20.0)	0	1 (20.0)	4 (6.7)	13 (11.2)
Withdrew consent	0	0	0	0	0	0	0	0	1 (1.7)	1 (0.9)
Progressive disease clinical	1 (33.3)	1 (16.7)	2 (33.3)	1 (14.3)	0	1 (6.7)	1 (14.3)	1 (20.0)	1 (1.7)	9 (7.8)
Progressive disease radiologic	0	1 (16.7)	0	1 (14.3)	1 (14.3)	2 (13.3)	1 (14.3)	0	6 (10.0)	12 (10.3)
Progressive disease – Richter's	2 (66.7)	3 (50.0)	2 (33.3)	1 (14.3)	0	2 (13.3)	0	0	5 (8.3)	15 (12.9)
Other	0	0	1 (16.7)	0	0	2 (13.3)	1 (14.3)	0	6 (10.0)	10 (8.6)

a. Additional subjects were enrolled in cohort 6 at 600 mg due to sites waiting for IRB/IEC approval of Protocol Amendment 6 in order to dose subjects at 800 mg.

b. After a fatality at 1200 mg in the setting of TLS (Subject 167, refer to Table 79) subjects dosing at 800 mg and 1200 mg were dose reduced to 600 mg or less. Two subjects in cohort 8 (Subjects 168 and 171; Appendix 16.2__5.1) did not escalate above 150 mg/day per investigator discretion.

Cross reference: Table 14.1__1.1.1, Tables 14.1__3.2.1.1 through 14.1__3.2.1.3, Table 14.1__3.2.1.8, Tables 14.1__3.3.1.1 through 14.1__3.3.1.3, Table 14.1__3.3.1.8

The percentage of Richter's transformation seems rather high.

Data Sets Analyzed

All 116 CLL/SLL subjects enrolled in the study received at least 1 dose of venetoclax and are included in the efficacy and safety analyses.

Efficacy results

Table 15: Summary of Response – CLL/SLL Subjects (per Investigator assessment)

Data cut-off 10 Feb 2015

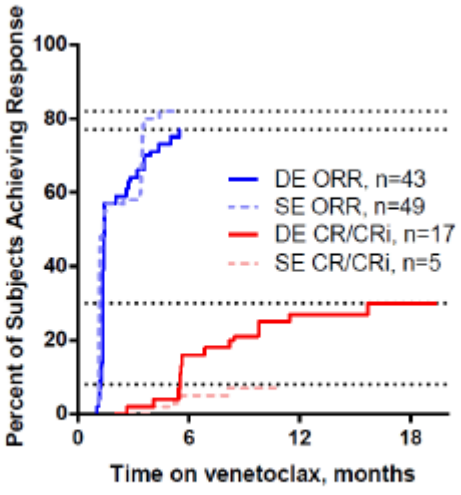
	Number of Subjects (%), [95% CI][a]				
Subject Response[b]	Dose Escalation Cohorts N = 56	Safety Expansion Cohort N = 60	Dose Cohorts < 400 mg N = 22	Dose Cohorts = 400 mg N = 67	Dose Cohorts > 400 mg N = 27
Overall response rate (CR + CRi + nPR + PR)	43 (76.8) [63.6, 87.0]	49 (81.7) [69.6, 90.5]	14 (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[d] (4.5)	2[e] (3.0)	2[f] (7.4)

CI = confidence interval; CR = complete remission; CRi = complete remission/incomplete bone marrow recovery; nPR = nodular partial remission; PR = partial remission

Per investigator assessment, ORR was somewhat less in dose cohorts <400 mg than in cohorts ≥400 mg, whereas only a very small difference was seen between cohorts on 400 mg and >400 mg. Note the reported high CR/Cri rate in the >400 mg cohort.

Time to response

Figure 10: Cumulative Response Over Time – CLL/SLL Subjects

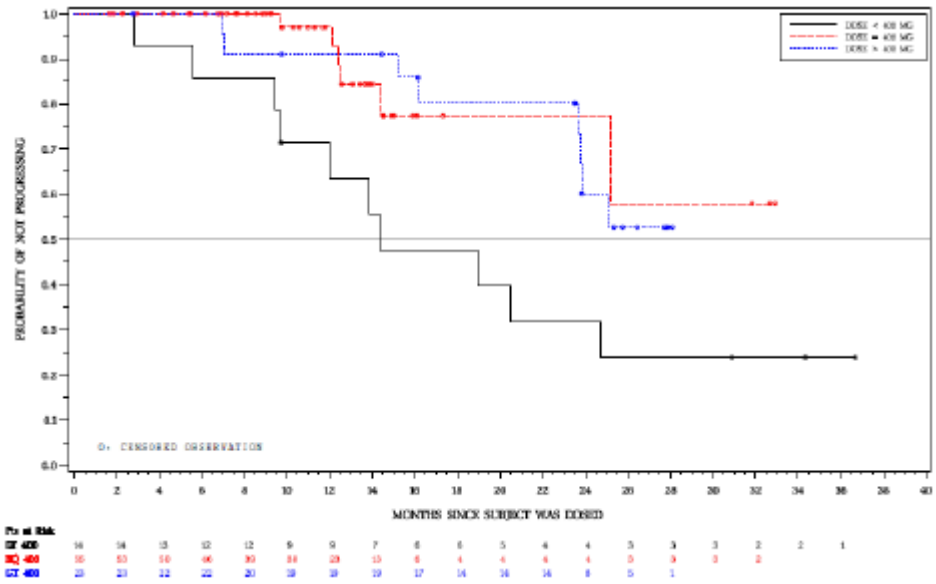


DE = dose escalation; CR = complete remission; CRi = complete remission/incomplete bone marrow recovery; ORR = overall response rate; SE = safety expansion

The time to first response was usually <2 months whereas time to CR varies between ~4 and ~16 months.

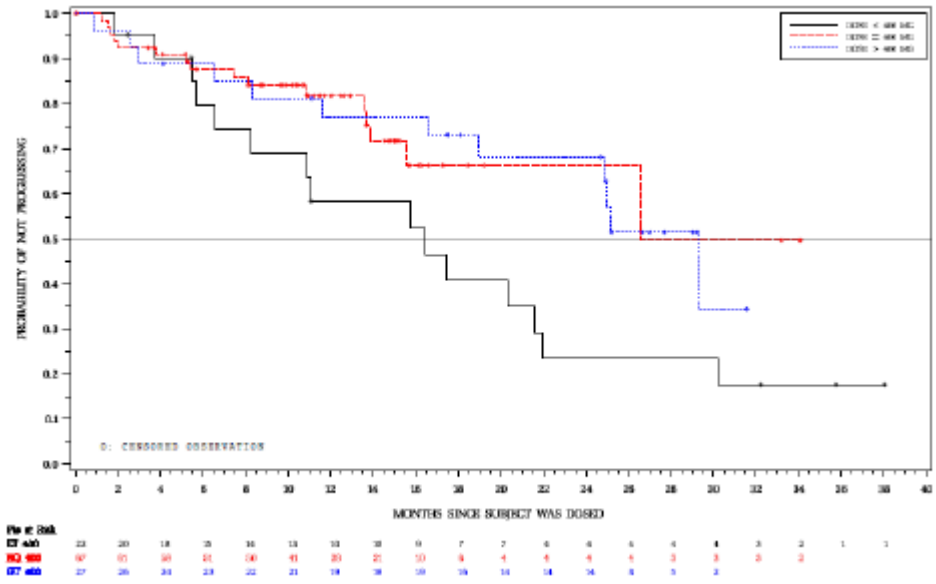
Duration of response

Figure 11: Kaplan-Meier Plot of Duration of Overall Response in Dose Cohorts of < 400 mg, =400 mg, and > 400 mg – CLL/SLL Subjects



Progression free survival

Figure 12: Kaplan-Meier Plot of Progression-Free Survival in Dose Cohorts of < 400 mg, = 400 mg, and > 400 mg – CLL/SLL Subjects



The DOR and PFS curves for dose cohorts <400 mg apparently separate from those of the ≥400mg cohorts.

IRC Assessment of Efficacy Endpoints

Overall Response Rate

A total of 59 subjects with CLL and 8 subjects with SLL received 400 mg venetoclax. Fifty-seven subjects with R/R CLL who had received 400 mg of venetoclax were reviewed by the IRC. Two subjects with CLL did not have complete baseline computed tomography (CT) assessments and were not reviewed by the IRC. The 8 subjects with SLL were not included in the IRC review to maintain a more homogenous population. These exclusions seem acceptable.

Summary of Response – CLL/SLL Subjects (Data cut-off 10 Feb 2015 and 28 Nov 2015)

	n (%) [95% CI]				
	All CLL/SLL Subjects		**CLL Subjects**		
	Updated Results[a]	**Previous Results[b]**	**Updated Results[a]**	**Previous Results[b]**	
	N = 67	**N = 67**	**N = 57**	**N = 57**	**N = 57**
Subject Response	**Investigator Assessed**	**Investigator Assessed**	**Investigator Assessed**	**Investigator Assessed**	**IRC Assessed**
Objective response rate [95% CI]	55 (82.1) [70.8, 90.4]	55 (82.1) [70.8, 90.4]	46 (80.7) [68.1, 90.0]	46 (80.7) [68.1, 90.0]	42 (73.7) [60.3, 84.5]
Complete remission rate (CR + CRi) [95% CI]	7 + 1 (11.9) [5.3, 22.2]	5 + 2 (10.4) [4.3, 20.3]	6 + 1 (12.3) [5.1, 23.7]	5 + 2 (12.3) [5.1, 23.7]	2 + 2 (7.0) [1.9, 17.0]
Nodular partial remission	2 (3.0)	2 (3.0)	2 (3.5)	2 (3.5)	0
Partial remission	45 (67.2)	46 (68.7)	37 (64.9)	37 (64.9)	38 (66.7)

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

Duration of ORR and PFS (10 Feb 2015)

For the 57-subject sample of R/R CLL subjects, the median DOR and PFS per investigator assessment are 40.1 months (95% CI: 24.0, NA) and 40.4 months (95% CI: 17.1, NA), respectively. Current estimates for DOR and PFS at 12 months are 95.1% and 80.2%.

Examination of Subgroups based on Investigator Assessments

Response was observed across all subgroups in analyses of ORR, CR, and PR among CLL/SLL subjects. Notably, responses were seen in patients with poor prognostic features, including 17p deletion, fludarabine-refractory, and IGVH unmutated. Exploratory analysis of *TP53* gene status also suggests a response in subjects with the mutated gene.

In addition, five study subjects had failed treatment with B-cell receptor inhibitors (i.e., ibrutinib and idelalisib for 2 subject each duvelisib for 1 subject) at study enrollment. All 5 had discontinued the study at the time of the data cutoff for this interim CSR. Best response, as assessed by their investigator, was PR for 2 subjects who had been treated with venetoclax for 184 and 421 days and stable disease for 2 subjects who had been treated with venetoclax for 56 and 170 days.

Results for subjects who previously failed therapy with BCR inhibitors should be compared (or combined) with those of study Study M14-032.

Efficacy correlation to dose level (Data cut-off 10 Feb 2015)

A greater proportion of subjects treated in cohorts assigned daily doses of 400 mg (82.1%) or higher (85.2%) achieved ORR, as compared to subjects assigned to treatment with a dose below 400 mg/day (63.6%). The estimated proportion of subjects with PFS at 12 months was 72.5% (95% CI: 58.0, 82.8) in the dose escalation cohorts. Subjects in dose cohorts less than 400 mg had lower estimated 12 month PFS (58.4%) than those in 400 mg (81.8%) or higher dose cohorts (77.1%).

Please also refer to the apparent exposure activity relationship discussed in the PD section above.

Safety

Adverse events were slightly higher at doses higher than 400 mg but no clear pattern was seen.

The 3 most common adverse events of all grades reported for CLL/SLL subjects, irrespective of severity or relationship to study drug, were diarrhoea (49.1%), nausea (47.4%), and neutropenia (44.8%). Diarrhea was reported in 48.3% (29/60) of subjects in the 400 mg safety expansion cohort and 46.7% to 60.0% of subjects at doses of 600 mg to 1200 mg. The incidence of nausea was 40.0% (24/60) in the 400 mg safety expansion cohort and 53.3% to 71.4% in the dose cohorts of 600 mg or higher. Neutropenia was observed in 41.7% (25/60) of subjects in 400 mg safety expansion cohort and ≥ 57.1% of subjects in dose cohorts of 600 mg or higher.

Dose-Limiting Toxicity – CLL/SLL

Of 116 CLL/SLL subjects enrolled in 7 dose-escalation cohorts and 1 safety expansion cohort, 6 experienced DLTs within the evaluable period for dose escalation purposes and 3 subjects had dose limiting events beyond that time frame.

Three subjects enrolled in cohort 1, at starting doses of both 100 and 200 mg, all had a DLT event of grade 3 TLS, and 2 of the events were considered serious. The events resolved in all 3 subjects. Two additional subjects experienced DLTs of TLS during dose escalation: one subject in cohort 4 (300 mg) who experienced a serious grade 4 TLS event accompanied by acute renal failure on Day 2 (50 mg starting dose); and, one subject in cohort 8 who experienced sudden death in the setting of TLS at the maximum designated cohort dose (1200 mg). Additionally, 1 subject (Subject 155, cohort 6 at 50 mg) experienced a DLT of nonserious, grade 4 neutropenia during dose escalation.

Since < 33% of subjects enrolled at each dose level after cohort 1 experienced a DLT dose escalation of the designated cohort dose in CLL/SLL subjects was continued in this study.

Three subjects had dose limiting events after the dose escalation period. One subject 120 (cohort 5 at 400 mg) had grade 2 thrombocytopenia which progressed to grade 4 and led to discontinuation of venetoclax, one subject in the same cohort experienced grade 2 vomiting and grade 3 muscle spasms that led to venetoclax dose interruption and reduction, and one subject in the safety expansion cohort experienced grade 3 neutropenia at 300 mg that did not result in any change to venetoclax dosing.

MTD was not determined for either arm A or B based on criteria prospectively defined in the protocol. The RPTD for CLL/SLL subjects was determined to be 400 mg based on data from all CLL/SLL subjects in the dose escalation cohorts.

2.5.2. Main study

Main study M13-982: A Phase 2 Open-Label Study of the Efficacy of ABT-199 (GDC-0199) in Subjects with Relapsed/Refractory or Previously Untreated Chronic Lymphocytic Leukaemia Harboring the 17p Deletion.

Methods

Study Participants

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 have 17p deletion assessed by 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.

Key Inclusion criteria

- Subject was ≥ 18 years of age.
- Subject had diagnosis of CLL according to 2008 Modified Guidelines from the International Workshop for Chronic Lymphocytic Leukaemia (IWCLL) NCI-WG.
- Subject had the 17p deletion
- Subject had an indication for treatment according to the 2008 Modified IWCLL NCI-WG Guidelines.
- Subject had clinically measurable disease (defined in Protocol Amendment 2)
- Subject had to have relapsed/refractory CLL (Protocol Amendments 1 through 3) or previously untreated CLL (Protocol Amendment 3, 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 [Protocol Amendments 2 and 3, safety expansion cohort] or had completed at least 2 cycles of treatment for a given line of therapy [Protocol Amendment 1]).

  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 (e.g., 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 an Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 2.
- Subjects were to have adequate bone marrow, coagulation, renal and hepatic function per laboratory reference range at screening.

Key Exclusion criteria

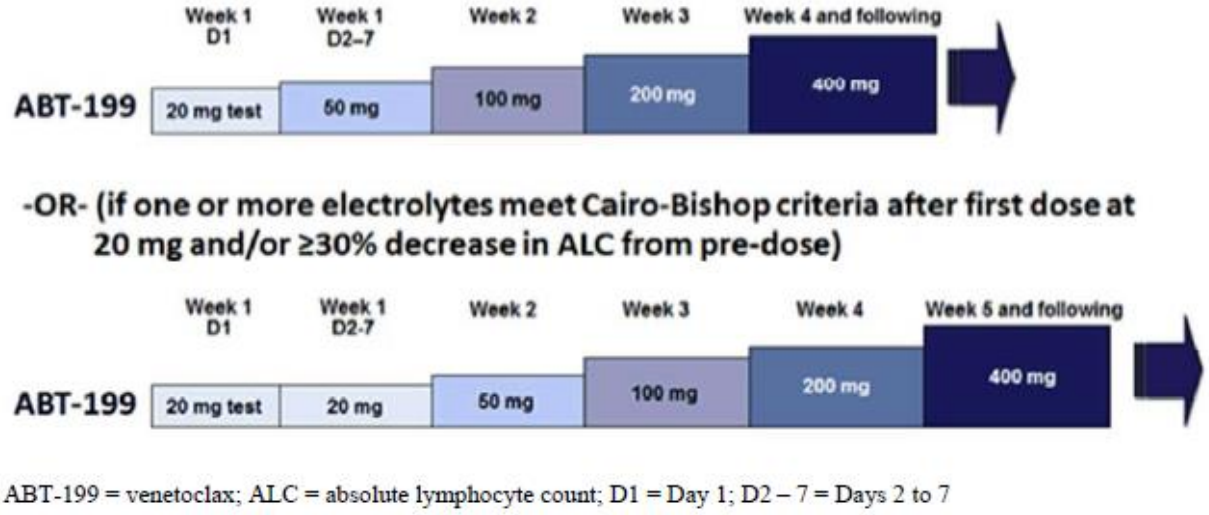
- Subject had undergone an allogeneic stem cell transplant.
- Subject had developed Richter's transformation
- (Added starting with Protocol Amendment 2 for safety expansion cohort only): Subject had prolymphocytic leukaemia.
- Subject had a known allergy to both xanthine oxidase inhibitors and rasburicase.
- Subject had active and uncontrolled autoimmune cytopenias
- Subject had received the following within 8 weeks (Protocol Amendment 1, main cohort) or within 30 days (starting with Protocol Amendment 2, safety expansion cohort) prior to the first dose of study drug: A biologic agent (i.e., monoclonal antibodies) for anti-neoplastic intent.
- Subject had received any of the following within 14 days (Protocol Amendment 1, main cohort) or within 5 half-lives (Protocol Amendment 2, safety expansion cohort) or within 14 days or 5 half-lives (Protocol Amendment 3, 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:
    - Any anticancer therapy including chemotherapy, or radiotherapy.
    - Investigational therapy, including targeted small molecule agents.
- Steroid therapy for anti-neoplastic intent was not allowed either during or within 7 days prior to the first dose of study treatment; allowable exceptions to steroid therapy were inhalational steroids for the treatment of asthma or chronic obstructive pulmonary disease, topical steroids, and/or replacement corticosteroid therapy for an inherited or acquired deficiency. In addition, (starting with Amendment 2), limited corticosteroid treatment (i.e., for approximately 21 days with rapid taper) was allowed while on study for significant active autoimmune cytopenias (e.g., AIHA or ITP).

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.

Venetoclax was administered orally once daily (QD), continuously. 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 hours, 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 hours 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 following dose escalation proceeded with weekly increases in dose: → 100 mg → 200 mg → 400 mg, as tolerated. Subjects may continue to receive venetoclax for up to 2 years following the date of the last subject enrolled, provided they continue to tolerate drug and have no evidence of disease progression.

Figure 13: Dosing schematic-Main cohort.



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

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, 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 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. The safety and tolerability of venetoclax in subjects with relapsed or refractory CLL harbouring 17p deletion was also evaluated.

Outcomes/endpoints

Primary efficacy analysis:

The assessment of ORR by IRC was performed once after 107 subjects had completed the 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.

Non-responders: Among these 70 subjects, those who had not achieved a CR, CRi, nPR, or confirmed PR prior to the data cut-off date.

Secondary Efficacy Analyses

Secondary efficacy endpoints will include all 107 subjects for ORR [NB. regarded as primary endpoint in this overview], complete remission rate (CR + CRi), partial remission rate (nPR + PR), duration of overall response (DoR), progression free survival (PFS), event free survival (EFS), time to progression (TTP), time to 50% reduction in absolute lymphocyte count (ALC), overall survival (OS), and percent of subjects who move on to stem cell transplant.

Duration of overall response DoR will be defined as the number of days from the date of first response (CR, CRi, nPR, or PR) by either CT scan or physical exam determination to the earliest recurrence PD or death per the IRC assessment. For subjects who have a PR before CR, CRi, or nPR in subsequent visits the DoR is computed from the earliest PR. For subjects who never experience response the

subject's data will not be included in the analysis. Duration of overall response will be analysed by Kaplan Meier methodology.

Additional Exploratory Efficacy Analyses

The additional exploratory efficacy analyses will be performed on the All Treated Subjects in the Main Cohort analysis set and All Treated Subjects in the Main Cohort with 17p Deletion CLL analysis set.

Descriptions of the additional efficacy endpoints are as follows:

Time to next anti-leukaemia treatment will be defined as the number of days from the date of the first dose to the date of first dose of new non protocol anti-leukaemia therapy (NPT) or death from any cause.

The rate of MRD response in subjects will be defined as the proportion of subjects who had MRD negative status. Only subjects with an MRD assessment negative or positive as required per protocol will be used in calculation of MRD response rate, indeterminate samples will not be included in the denominator for the calculation.

Health Economic and Patient Reported Outcome measures will include the MD Anderson Symptom Inventory (MDASI) measure of patient reported symptoms the EORTC QLQ C30 and QLQ CLL16 and the EQ-5D-5L, and EQ 5D VAS.

Sample Size

Approximately 100 subjects were planned 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 adverse event occurs at a rate of 2%, then the probability of observing at least 1 event in a trial with 100 subjects is 86%.

Performing the efficacy analyses at 70 subjects provides at least 90% power (at two-sided alpha of 5%) to reject the null hypothesis of 40% ORR in favor of an alternative hypothesis of 60% ORR. Concerning safety signals detection 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. For the safety expansion cohort, an additional 50 subjects will 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 occurs at a rate of 2%, then the probability of observing at least 1 event in this cohort of 50 subjects is 64%.

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. 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.

Randomisation

This was a single arm study.

Blinding (masking)

There was no blinding in the study.

Statistical methods

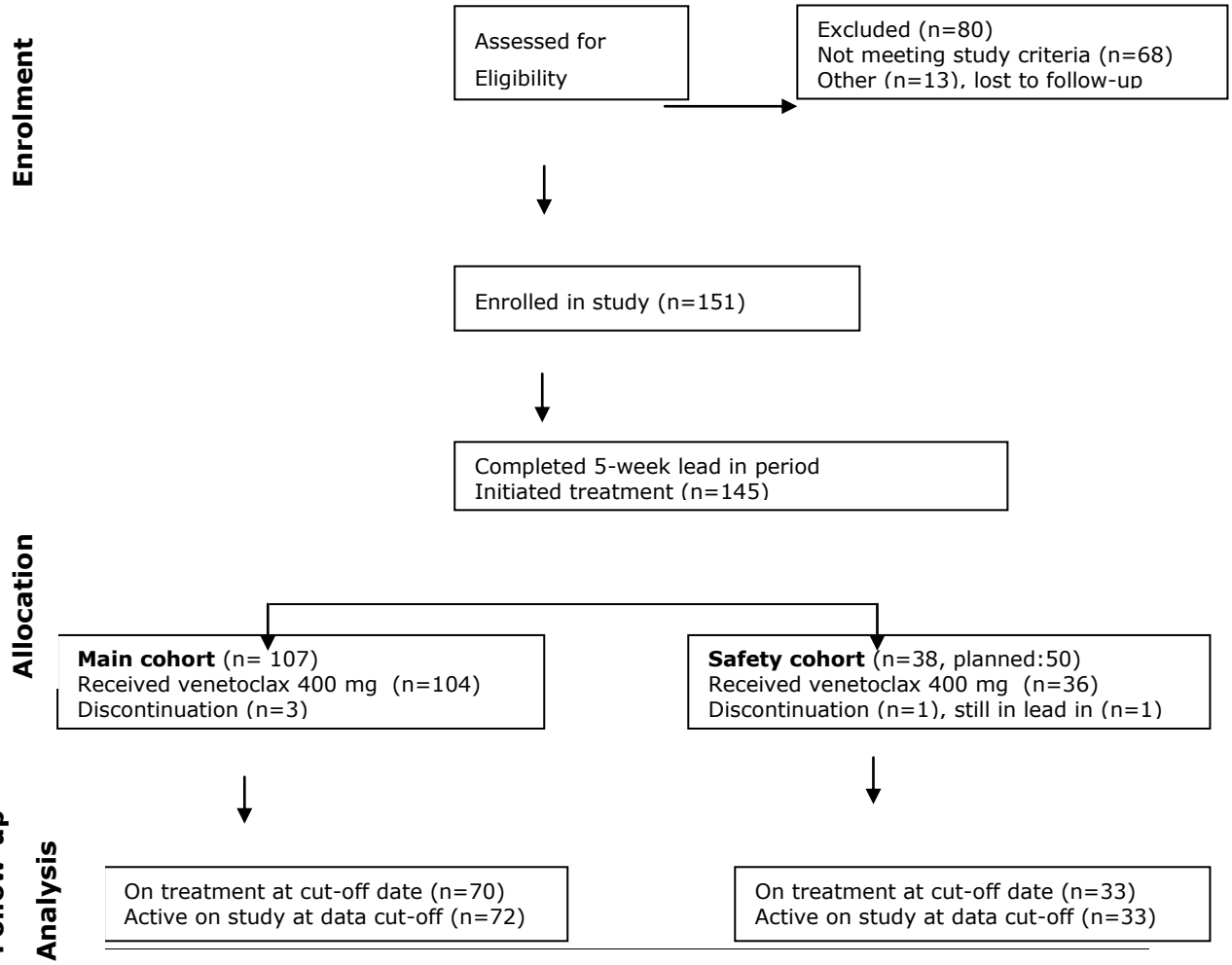
Descriptive statistics were planned. For binary endpoints (e.g. ORR), 95%-CI were calculated according to the Pearson-Clopper method. Kaplan-Meier methods were used for time-to-event endpoints (such as PFS, OS).

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 enrollment plus 1 day.

Only one test Multiplicity (primary analysis for ORR in the main cohort efficacy) was planned. Descriptive statistics and 95%-CI for all other endpoints were included. As interim analysis one safety review by independent data monitoring committee when 20 patients had completed at least 12 week of treatment.

Results

Participant flow



Recruitment

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. 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.

Conduct of the study

Protocol deviations were defined in accordance with ICH guidelines. In addition, TLS prophylaxis and management deviations were assessed. All deviations were assessed for impact on analyses and data integrity.

There was a total of 114 protocol deviations (PDs), of which 50 were classified as medically significant, noted in the main cohort. None of the PDs were considered to have affected the study outcome or interpretation of the study results or conclusions.

Protocol Changes

Three protocol amendments were issued during the conduct of this study as of the study cut-off date.

No subjects were enrolled under the original protocol. Protocol Amendment 1 was dated 10 May 2013. A total of 107 subjects (comprising the main cohort) were enrolled under this Amendment. The main purpose of the amendment was to implement more stringent measures (referred to as "Post May 2013" measures) for prophylaxis and management of TLS.

Protocol Amendment 2 was dated 25 July 2014. A total of 36 subjects (all in the safety expansion cohort) were enrolled under this Amendment. The revised measures included a starting dose of 20 mg and 5 step ramp-up to 400 mg, less stringent TLS prophylaxis and monitoring (referred to as "Current" measures) depending on the risk category, and the addition of a safety expansion cohort to evaluate these measures.

Protocol Amendment 3 was dated 19 December 2014. The main purpose of the amendment was to include subjects in the study with previously untreated CLL harboring 17p deletion in the Safety Expansion Cohort. As of the data cutoff date for this interim report, total of 2 subjects (in the safety expansion cohort) were enrolled under this Amendment [and are not included in the efficacy analysis].

Baseline data

The mean age was 66y and male patients constituted ~63 %. The vast majority of the study population (~97%) were white, and approx. 65% were from the EU. Mean/median number of prior therapies was 2.8/2.

Table 16: Disease Stage at Diagnosis and Baseline Eastern Cooperative Oncology Score – All Treated Subjects

Category Characteristic	Main Cohort (N = 107) n (%)	Safety Expansion Cohort (N = 38) n (%)	Total (N = 145) n (%)
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)
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)

At diagnosis, most subjects had limited (Rai/Binet-) disease stage (meaning enlarged lymph nodes and/or enlargement of spleen and/or liver, but near normal RBC and platelet counts) and ~92% had ECOG ≤1. Considering the mean time since diagnosis of ~7.5 years (see below), the respective stage at baseline would have been more relevant.

Although Rai and Binet staging has not been presented at study initiation, the assessment of the tumour burden indicates that patients with a variety of disease staging and progressive disease are included. The TLS risk categories, as defined by tumour burden and total lymphocytes, classified 23.4% subjects in low, 38% subjects in intermediate and 38.7% of the subjects of the main cohort in the high risk category.

Chromosomal Aberrations

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)			
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

All subjects enrolled in the study were to harbour the 17p deletion. Due to an error at the study site, 1 subject was enrolled who did not meet the 17p deletion assay cut-off of > 7%. The subject's data are included in all analyses.

Baseline Prognostic Factors – All Treated Subjects

Category Characteristic	Main Cohort (N = 107) n (%)	Safety Expansion Cohort (N = 38) n (%)	Total (N = 145) n (%)
ZAP-70			
Positive	16 (27.1)	7 (46.7)	23 (31.1)
Negative	13 (22.0)	4 (26.7)	17 (23.0)
Indeterminate	30 (50.8)	4 (26.7)	34 (45.9)
Missing	48	23	71
CD38			
Positive	28 (36.8)	10 (45.5)	38 (38.8)
Negative	28 (36.8)	9 (40.9)	37 (37.8)
Indeterminate	20 (26.3)	3 (13.6)	23 (23.5)
Missing	31	16	47
IgV_H			
Mutated	7 (18.9)	4 (28.6)	11 (21.6)
Unmutated	30 (81.1)	10 (71.4)	40 (78.4)
Missing	70	24	94
Fludarabine Refractory[a]			
Yes	34 (37.4)	7 (18.9)	41 (28.3)
No	57 (62.6)	30 (81.1)	87 (60.0)
Missing	16	1	17
Bulky Disease			
No nodes ≥ 5 cm	50 (46.7)	24 (63.2)	74 (51.0)
One or more nodes ≥ 5 cm	57 (53.3)	14 (36.8)	71 (49.0)
No nodes ≥ 10 cm	90 (84.1)	35 (92.1)	125 (86.2)
One or more nodes ≥ 10 cm	17 (15.9)	3 (7.9)	20 (13.8)
Creatinine Clearance			
< 60 mL/sec	50 (46.7)	15 (39.5)	65 (44.8)
≥ 60 – < 90 mL/sec	42 (39.3)	19 (50.0)	61 (42.1)
≥ 90 mL/sec	15 (14.0)	4 (10.5)	19 (13.1)
Months from Diagnosis to First Dose			
N	106	38	144
Mean (SD)	94.0 (72.40)	87.1 (63.40)	92.2 (69.99)
Median	81.7	70.9	77.2
Min – Max	1.2 – 385.6	5.6 – 222.8	1.2 – 385.6

IgV_H = immunoglobulin variable-region heavy-chain; ZAP70 = zeta chain-associated protein kinase 70 kDa

CD38, IgV_H, and ZAP70 statuses, based on results from site's local laboratories.

Percentages calculated on non-missing values unless otherwise stated.

a. Fludarabine refractory status as reported by the investigator.

Cross reference: Table 14.1__4.1.1, Table 14.1__4.2.1

Among other negative prognostic factors, it is noted that 28.3% were reported as being fludarabine refractory per investigator assessment (37% in the main cohort) and 49% had one or more nodes ≥5 cm. Mean and median time since diagnosis >7years and >6 years, respectively, perhaps illustrating that del17p often is a manifestation of advanced and late stage disease in CLL.

The significance of these additional risk factors in CLL with 17pdel is not known.

Baseline Assessment of Tumour Lysis Syndrome Risk

Subjects were classified in 3 protocol-defined risk categories based on the risk for developing TLS as defined by tumour burden and total lymphocytes.

Baseline Assessment Per Investigator of Tumour Lysis Syndrome Risk – All Treated Subjects

Tumor Lysis Syndrome Risk Category	Main Cohort (N = 107) n (%)	Safety Expansion Cohort (N = 38) n (%)	Total (N = 145) n (%)
Low	19 (17.8	14 (36.8)	33 (22.8)
Medium	43 (40.2)	12 (31.6)	55 (37.9)
High[a]	45 (42.1)	12 (31.6)	57 (39.3)

The majority of subjects were classified as medium or high risk for TLS.

Numbers analysed

For this interim report, the efficacy analyses were performed for subjects in the main cohort only (total efficacy population, n=107). Efficacy analyses for all subjects, including the safety expansion cohort, will be included in the final report for this study.

Further updates of study results will provide data from up to approx. 50 additional patients (from the safety expansion cohort) and will increase data maturity.

Outcomes and estimation

Primary endpoint Response Rate

Table 17: Overall Response (Data cut-off 30 April 2015 and 29 January 2016)

	n (%) [95% CI]				
	Updated Results[a]			**Previous Results[b]**	
	SE Cohort N = 51	**Main Cohort N = 107[c]**	**Both Cohorts N = 158**	**Main Cohort N = 107[c]**	
Subject Response	**Investigator Assessed**	**Investigator Assessed**	**Investigator Assessed**	**Investigator Assessed**	**IRC Assessed**
ORR [95% CI]	42 (82.4) [69.1, 91.6]	80 (74.8) [65.4, 82.7]	122 (77.2) [69.9, 83.5]	79 (73.8) [64.4, 81.9]	85 (79.4) [70.5, 86.6]
CR rate (CR + CRi) [95% CI]	7 + 2 (17.6) [8.4, 30.9]	19 + 1 (18.7) [11.8, 27.4]	26 + 3 (18.4) [12.7, 25.3]	14 + 3 (15.9) [9.5, 24.2]	6 + 2 (7.5) [3.3, 14.2]
nPR rate	3 (5.9)	5 (4.7)	8 (5.1)	4 (3.7)	3 (2.8)
PR rate	30 (58.8)	55 (51.4)	85 (53.8)	58 (54.2)	74 (69.2)
Non-responder[d]	--	--	--	--	22 (20.6)
Stable disease	7 (13.7)	23 (21.5)	30 (19.0)	24 (22.4)	--[d]
Disease progression	1 (2.0)	2 (1.9)	3 (1.9)	2 (1.9)	--[d]
Incomplete data	1 (2.0)	2 (1.9)	3 (1.9)	2 (1.9)	--[d]

SE = safety expansion cohort; OR = objective response rate; CI = confidence interval (95% CI is from the exact binomial distribution); CR = complete remission; CRi = complete remission with incomplete marrow recovery; IRC = independent review committee; nPR = nodular partial remission; PR = partial remission

After prolonged follow-up, CR/CRi rates was increased whilst ORR remained stable.

Among the subjects achieving PR by IRC, 16 subjects showed absence of leukemic infiltrate in their bone marrow based on morphological and immunohistochemical (IHC) analysis (30 April 2015 cut-off).

Differences in ORR between the IRC and Investigator (30 April 2015 cut-off)

The ORR rate by IRC assessment was higher than that by investigator assessment. Primarily, this was a result of differences in interpretation of splenomegaly and hepatomegaly, which may have been affected by subjectivity in the assessment of the CT scans.

Deep responses (subjects with CR/CRi and nPR) by IRC assessment were lower than those by investigator assessment. Primarily, this was a result of differences in radiologic assessments (PR versus CR) based mainly on target lesion measurements. Of note, there were 10 subjects who were assessed as having complete remission by the study investigator, who were not considered CR by IRC assessment. In these 10 subjects, the PR assessments by the IRC were mainly based on node size > 15 mm. Of note, 2 of the 10 subjects were found to be MRD negative.

Differences in response assessments between the IRC and investigator were observed in 31 subjects. These differences showed no clear tendency of being more or less positive in either category but went in both directions, i.e. sometimes the IRC assessed PR where the investigator assessed SD, and sometimes the investigator assessed CR where IC assessed PR.

Secondary endpoints

Duration of Overall Response and Progression-free survival (Data cut-off 30 April 2015 and 29 January 2016)

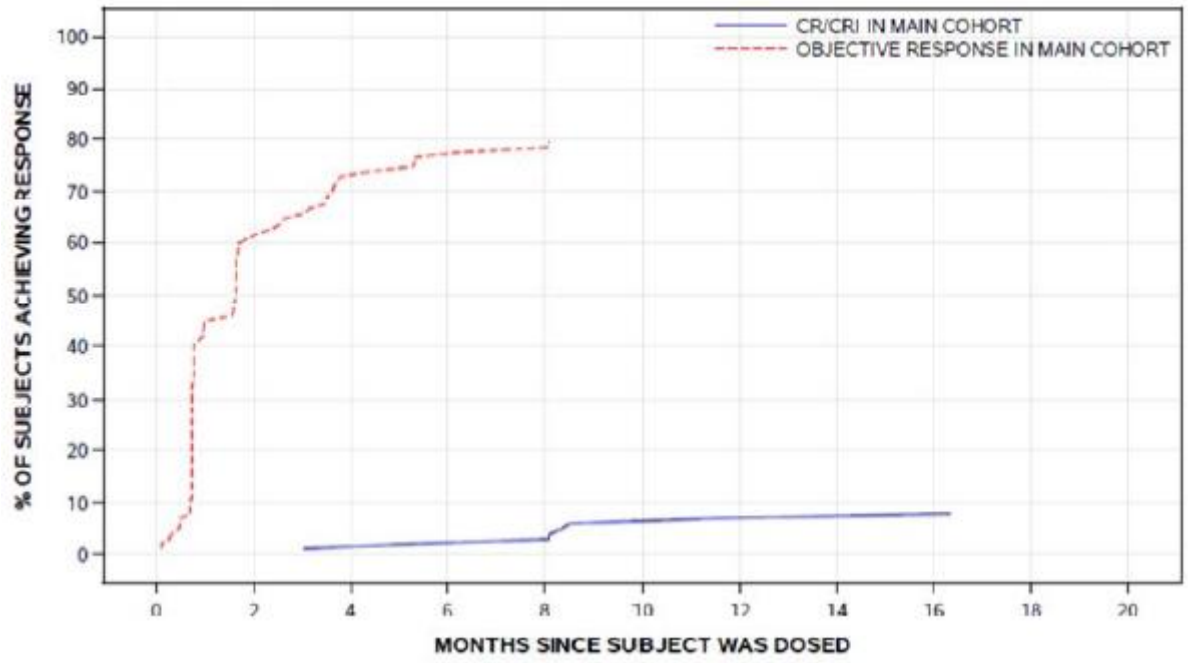
	Updated Results[a]			**Previous Results[b]**	
	SE Cohort N = 51	**Main Cohort N = 107[c]**	**Both Cohorts N = 158[c]**	**Main Cohort N = 107[c]**	
Endpoint	**Investigator Assessed**	**Investigator Assessed**	**Investigator Assessed**	**Investigator Assessed**	**IRC Assessed**
DOR	N = 42	N = 80	N = 122	N = 79	N = 85
Median[d]	NR	26.5 [22.7, --]	26.5 [22.7, --]	NR	NR
12 months[e]	92.3 [77.9, 97.4]	89.9 [80.9, 94.8]	90.3 [83.2, 94.6]	89.1 [79.2, 94.4]	84.7 [74.5, 91.0]
18 months[e]	NA	83.5 [73.3, 90.1]	83.9 [74.7, 89.9]	NA	NA
PFS	N = 51	N = 107	N = 158	N = 107[c]	N = 107
Median	NR	27.2 [19.7, --]	27.2 [21.9, --]	NR	NR
12 months	79.8 [65.6, 88.6]	74.9 [65.3, 82.1]	75.7 [67.9, 81.9]	74.6 [64.9, 81.9]	72.0 [61.8, 79.8]
18 months	NA	65.8 [55.7, 74.1]	66.7 [57.7, 74.2]	NA	NA

DOR = duration of response; NR = not reached; NA = not applicable; PFS = progression-free survival

Time to First Response

First response (CR or PR) was observed at the first visit for most subjects in the main cohort with a median of 0.8 months (range: 0.1 to 8.1). A notable increase in the CR/CRi rate was observed at the disease assessment at 36 weeks (8.3 months) consistently with the protocol-required radiologic assessment as well as with bone marrow assessment, in eligible subjects.

Figure 14: Cumulative Response Rate Over Time – IRC Assessment (Data cut-off 30 April 2015)



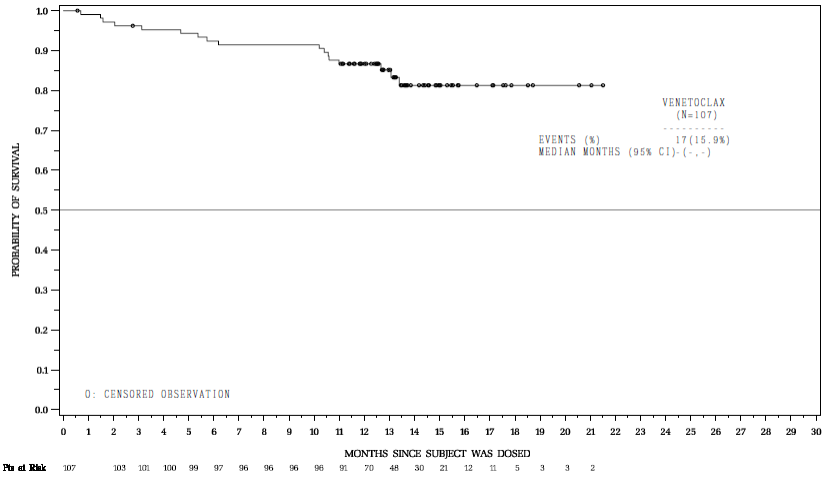
Time to 50% Reduction in Absolute Lymphocyte Count

Eighty-seven (81.3%) subjects had lymphocytosis at baseline, defined as the presence of absolute lymphocyte count of > 5 × 10^9/L and only these subjects were assessed for this secondary objective.

A total of 85 of 87 subjects had a 50% reduction in ALC, occurring on average within the first week of treatment (median 0.3 months [range: 0.1 to 0.9 months]). Notably, 53 subjects had their lymphocyte count normalized to < 4 × 10^9/L by Week 4. Of the 2 subjects not having a reduction in ALC of 50%, 1 subject withdrew consent after 1 day of treatment with venetoclax, and 1 subject, with a stable disease, progressed after Week 20.

Hence, the vast majority of patients had a 50% reduction in ALC, usually within the first couple of weeks. This is different from the pattern generally seen with BCRi in CLL, where many patients respond with an increase in ALC (or with a sustained elevation of ALC in spite of response in lymph nodes and other manifestations).

Figure 15: Kaplan-Meier plot of Overall survival (main cohort)



A total of 17 (15.9%) subjects in the main cohort died. 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

Three (3; 2.8%, all responders) of subjects in the main cohort subsequently received a stem cell transplant. 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.

Summary of Previously Submitted and Updated MRD Results from the Main Cohort

	n (%)	
	Updated Results[a]	**Previous Results[b]**
	N = 107[c]	**N = 107[c]**
Subjects tested (peripheral blood or bone marrow)	63 (58.9)	45 (42.1)
MRD negative by peripheral blood	28 (26.2)	18 (16.8)
MRD negative by bone marrow	11 (10.3)	6 (5.6)

a. Data cut-off for updated results: 29 January 2016.

b. Data cut-off for previously reported results: 30 April 2015.

c. Includes the one subject not confirmed to have 17p del status.

MRD Results from the Safety Expansion Cohort of Study M13-982

	n (%)	
	Updated Results[a]	
	SE Cohort N = 51	**Both Cohorts N = 158**
Subjects tested (peripheral blood or bone marrow)	40 (78.4)	103 (65.0)
MRD negative by peripheral blood	10 (19.6)	38 (24.1)
MRD negative by bone marrow	5 (9.8)	16 10.1)

a. Data cut-off for updated results: 29 January 2016.

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.

Patient-reported health related QoL measures

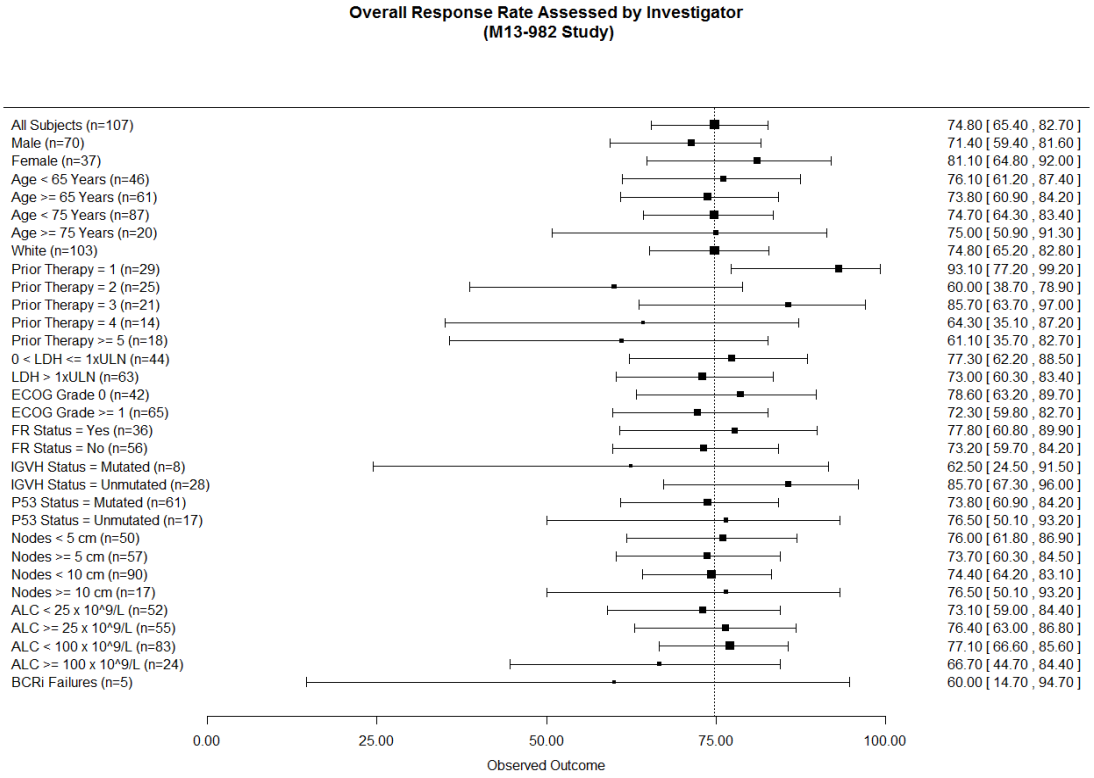
Patient-reported health related QoL measures were identified as exploratory efficacy endpoints for this study, including MDASI, EORTC QLQ-C30, EORTC QLQ-CLL16, EQ-5D-5L, and EQ VAS.

Subjects seemed to do better in symptoms and QoL on venetoclax during the course of the study compared to their baseline value. No net negative and significant changes were noted.

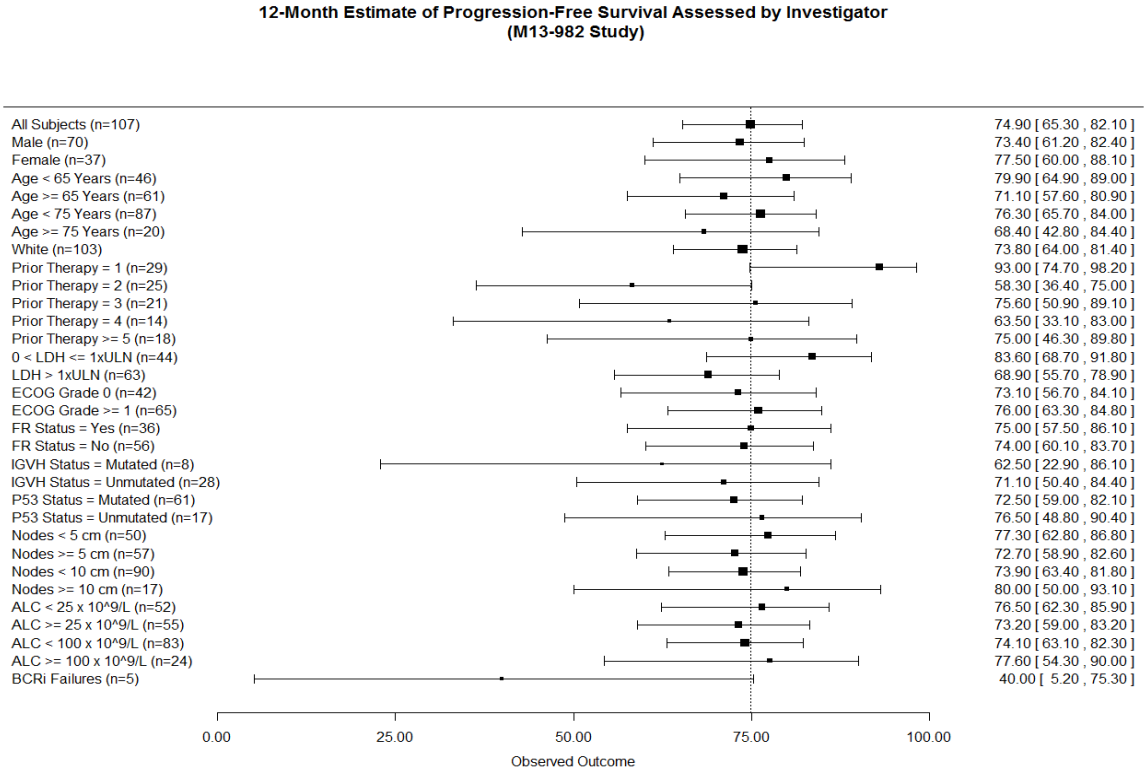
Ancillary analyses

Efficacy in Subgroups

Overall Response Rate (Study M13-982)



12-Month Estimate of PFS (Study M13-982)



Updated results

Study M13-982 Investigator Assessed Responses (10 June 2016, 29 Jan. 2016)

	n (%) [95% CI]					
	Updated Results[a]			Previous Results[b]		
Subject Response	SE Cohort N = 51	Main Cohort N = 107[c]	Both Cohorts N = 158[c]	SE Cohort N = 51	Main Cohort N = 107[c]	Both Cohorts N = 158[c]
ORR	42 (82.4) [69.1, 91.6]	80 (74.8) [65.4, 82.7]	122 (77.2) [69.9, 83.5]	42 (82.4) [69.1, 91.6]	80 (74.8) [65.4, 82.7]	122 (77.2) [69.9, 83.5]
CR rate (CR + CRi)	7 + 1 (15.7) [7.0, 28.6]	20 + 1 (19.6) [12.6, 28.4]	27 + 2 (18.4) [12.7, 25.3]	7 + 2 (17.6) [8.4, 30.9]	19 + 1 (18.7) [11.8, 27.4]	26 + 3 (18.4) [12.7, 25.3]
nPR rate	4 (7.8)	5 (4.7)	9 (5.7)	3 (5.9)	5 (4.7)	8 (5.1)
PR rate	30 (58.8)	54 (50.5)	84 (53.2)	30 (58.8)	55 (51.4)	85 (53.8)
Stable disease	7 (13.7)	23 (21.5)	30 (19.0)	7 (13.7)	23 (21.5)	30 (19.0)
Disease progression	1 (2.0)	2 (1.9)	3 (1.9)	1 (2.0)	2 (1.9)	3 (1.9)
Incomplete data	1 (2.0)	2 (1.9)	3 (1.9)	1 (2.0)	2 (1.9)	3 (1.9)

SE = safety expansion cohort; ORR = objective response rate; 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 cut-off for updated results: 10 June 2016.

b. Data cut off for previously reported results: 29 January 2016.

c. Includes the one subject not confirmed to have 17p del status.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 18: Summary of efficacy for trial M13-982

Title: A Phase 2 Open-Label Study of the Efficacy of ABT-199 (GDC-0199) in Subjects with Relapsed/Refractory or Previously Untreated Chronic Lymphocytic Leukaemia Harboring the 17p Deletion.			
Study identifier	**M13-982**		
Design	Single arm		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		≤2 years (≥5 Wks ramp-up dosing) not applicable
Hypothesis	The ORR for venetoclax was tested to reject the null hypothesis of ORR 40%.		
Treatments groups	Main cohort		Venetoclax 400 mg QD. Mean treatment duration 12.1 months, n=107
	Safety cohort		Venetoclax 400 mg QD, n=38
Endpoints and definitions	Primary endpoint	ORR	Response rate
	Secondary	DOR	Duration of Overall Response (at 12 months)
	Secondary	PFS	Progression-Free survival (at 12 months)
		TTR	Time to first response
		50% red ALC	Time to 50% Reduction in Absolute Lymphocyte Count
		OS	Overall survival
Database lock	30 April 2015 (FPFV 27 June 2013) update 29 January 2016		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	(All subjects in the main cohort who received at least 1 dose of study drug were analysed for efficacy; n=107).			
Descriptive statistics and estimate variability	Treatment group	Main cohort	Main cohort	SE cohort
		30 April 2015	29 Jan 2016	29 Jan 2016
	Number of subject	107 (IRC)	107 (Inv.)	51 (Inv.)
	ORR	79 %	75%	82%
	95% CI	(71%; 87%)	(65%; 83%)	(69%; 92%)
	CR + CRi	16%	19%	18%
	95% CI	(8%; 31%)	(12%; 27%)	(8%; 31%)
	DOR at 12 months (K-M estimate %)	84.7%	90%	92%
		(75%, 91%),	(81%; 95%)	(78%: 97%)
	PFS at 12 months(K-M estimate %)	72%	75%	80%
	95% CI	(62%, 80%)	(65%; 82%)	(66%; 89%)
	Time to First Response **PR** **CR/CRi**	 0,8 months 8,2 months		
	50% red ALC	≤1 week		

	OS (K-M estimate % subjects surviving at 12 months)	86.7%		
	95% CI	(78.6%, 91.9%)		

Analysis performed across trials (pooled analyses and meta-analysis)
N/A

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	N/A		
Non Controlled Trials	213/592	77/592	4/592
Total monotherapy studies	152/379	60/379	3/379
M13-982	64/158	27/158	1/158
M12-175	47116	16/116	1/116
M14-032	4105	17105	1/105
Total combination studies	59/143	12/143	1/143
M13-365	20/49	7/49	2/49
GP28331	21/49	4/49	0/49
GO28440	18/45	1/45	0/45

Supportive studies
Study M14-032 (data cut off 10 February 2016)

Study M14-032 is an open-label, 2-arm, multi-centre study evaluating 400 mg of venetoclax in subjects with CLL who relapsed after or were refractory to treatment with either ibrutinib or idelalisib.

Arm A was targeted to enrol 40 subjects after receiving ibrutinib and Arm B was to enrol 20 subjects after receiving idelalisib treatment.

In Arm A, 26/43 (60.4%) subjects had refractory disease and 13 (30.2%) had progression after discontinuation of ibrutinib for toxicity.

In Arm B, 6/21 (28.6%) had refractory disease and 11 (52.3%) had progression after discontinuation of idelalisib for toxicity.

Discontinuation of previous ibrutinib or idelalisib treatment due to toxicity was predominantly for diarrhoea and pulmonary events in both arms. Median time on ibrutinib was 17 months (range: 1 – 56) and the median time on idelalisib was 8 months (range: 1 – 27).

Median age for subjects in Arm A is 66 (range: 48 – 80) with 26 (60.5%) subjects being ≥ 65 years of age. In Arm B the median age is 68 (range: 56 – 85) while 15 (71.4%) subjects are ≥ 65 years of age. Nine of the 64 subjects have received both ibrutinib and idelalisib; 4 of these subjects were enrolled into Arm A and 5 into Arm B based on their most recent treatment.

Venetoclax 400 mg Monotherapy Responses in Study M14-032

	n (%) [95% CI]			
	Updated Results[a]			
	ARM A Ibrutinib Failure N = 43		**ARM B Idelalisib Failure N = 21**	
Subject Response	**IRC Assessed**	**Investigator Assessed**	**IRC Assessed**	**Investigator Assessed**
Objective response rate [95% CI]	30 (69.8) [53.9, 82.8]	26 (60.5) [44.4, 75.0]	10 (47.6) [25.7, 70.2]	7 (33.3) [14.6, 57.0]
Complete remission rate (CR + CRi) [95% CI]	1 (2.3) [0.1, 12.3]	2 + 0 (4.7) [0.6, 15.8]	0 (0)	1 + 1 (9.5) [1.2, 30.4]
Non responder[c]	13 (30.2)	--	11 (52.4)	--
Stable disease	--[c]	12 (27.9)	--[c]	12 (57.1)
Disease progression	--[c]	1 (2.3)	--[c]	1 (4.8)
Incomplete data	--[c]	4 (9.3)	--[c]	1 (4.8)

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

a Data cut-off for updated results: 10 February 2016.

c Two subjects have reached the 8 week assessment only.

d Subjects with progressive disease, stable disease, or incomplete data were considered non-responders by the IRC.

6-Month Estimates for Secondary Endpoints of Study M14-032 (data cut-off 10 Feb. 2016)

	Updated Results[a]			
	ARM A Ibrutinib Failure		**ARM B Idelalisib Failure**	
Endpoint	**IRC Assessed**	**Investigator Assessed**	**IRC Assessed**	**Investigator Assessed**
Subject, N	N = 30	N = 26	N = 10	N = 7

DOR[b]	92.2 [71.8, 98.0]	90.9 [68.1, 97.6]	100	100
Time to first response[c]	1.6 [1.0, 5.5]	1.6 [1.6, 5.6]	1.6 [1.6, 2.2]	1.6 [1.6, 3.5]
Subject, N	N = 43	N = 43	N = 21	N = 21
PFS[b]	80.6 [64.8, 89.8]	88.1 [73.7, 94.9]	88.0 [59.4, 96.9]	87.7 [58.1, 96.9]
Overall survival[b]	90.6 [76.8, 96.4]		95.2 [70.7, 99.3]	

DOR = duration of response; IRC = independent review committee; PFS = progression-free survival

Data cut-off for updated results: 10 February 2016.

Updated results from Study M14-032 Full Study Population (10 June 2016, 10 February 2016)

	n (%) [95% CI]							
	ARM A Ibrutinib Failure N = 43				ARM B Idelalisib Failure N = 21			
	IRC Assessed		Investigator Assessed		IRC Assessed		Investigator Assessed	
	Previous[a]	Updated[b]	Previous[a]	Updated[b]	Previous[a]	Updated[b]	Previous[a]	Updated[b]
ORR	30 (69.8) [53.9, 82.8]	30 (69.8) [53.9, 82.8]	26 (60.5) [44.4, 75.0]	29 (67.4) [51.5, 80.9]	10 (47.6) [25.7, 70.2]	13 (61.9) [38.4, 81.9]	7 (33.3) [14.6, 57.0]	12 (57.1) [34.0, 78.2]
CR + CRi	0 + 1 (2.3)	0 + 1 (2.3)	2 + 0 (4.7)	2 + 1 (7.0)	0 (0)	0	1 + 1 (9.5)	2 + 1 (14.3)
nPR	0 (0)	0	2 (4.7)	2 (4.7)	0 (0)	0	0 (0)	0
PR	29 (67.4)	29 (67.4)	22 (51.2)	24 (55.8)	10 (47.6)	13 (61.9)	5 (23.8)	9 (42.9)
Non responder[c]	13 (30.2)	13 (30.2)	--	--	11 (52.4)	8 (38.1)	--	--
SD	--	--	12 (27.9)	9 (20.9)	--	--	12 (57.1)	8 (38.1)
DP	--	--	1 (2.3)	1 (2.3)	--	--	1 (4.8)	1 (4.8)
Incomplete data	--	--	4 (9.3)	4 (9.3)	--	--	1 (4.8)	0

CI = confidence interval (95% CI is from the exact binomial distribution); CR = complete remission; CRi = complete remission with incomplete marrow recovery; DP = disease progression; PR = nodular partial remission; ORR = objective response rate; PR = partial remission; SD = stable disease

a. Data are as of 10 February 2016.

b. Data are as of 10 June 2016.

c. Subjects with progressive disease, stable disease, or incomplete data were considered non-responders by the IRC.

Venetoclax in combination with rituximab Study M13-365

Study M13-365 is an ongoing dose-escalation study evaluating the safety and tolerability of venetoclax in combination with rituximab in subjects with relapsed CLL or SLL. The primary objectives were to assess the safety profile and to determine the MTD, RPTD, tolerability, and optimal lead-in period of venetoclax when administered in combination with rituximab. The secondary objectives were to assess the pharmacokinetic profile and efficacy of the combination. MRD in the bone marrow and blood were exploratory endpoints.

ORR for venetoclax in combination with rituximab was ~80%, which seems more or less the same as for venetoclax monotherapy, however, CR+CRi in ~35%, seems to indicate a higher proportion of deep responses.

2.5.3. Discussion on clinical efficacy

Four uncontrolled studies provide the basis to support efficacy of venetoclax in adult patients with chronic lymphocytic leukaemia (CLL) in the presence of 17p deletion or *TP53* mutations.

Design and conduct of clinical studies

In the pivotal M13-982, 106 patients (of a total 107) with del17p-CLL were enrolled in the main cohort. The median duration of treatment was 13 months (main cohort). In addition there is a safety expansion cohort (n=51). Study M14-032 is of major interest as the target population, subjects with CLL who have failed therapy with BCRi, constitutes a population with unmet medical need. Altogether 64 subjects were enrolled for a median study duration of 8 months. Study M12-175, is the key supportive study comprising 116 patients with R/R CLL. In this study, 36/116 had known high-risk criterion of del17p/TP53-mutation and 67/116 were treated with the [target] dose 400 mg. In addition, 5 of the enrolled subjects had failed previous therapy with BCR-inhibitors. Median duration of exposure was 19 months in the 400 mg cohort (n=67). Finally, study M13-365 is an ongoing Phase 1b study evaluating venetoclax in combination with rituximab in subjects with relapsed CLL or SLL. As of the data cut-off, a total of 49 subjects were enrolled and the median time on study was 10.3 months.

All the included studies in this MAA are single-arm which represents a weakness. In accordance with the CHMP scientific advice (January 2014) based on preliminary results from study M12-175 and lack of approved therapeutic alternatives at the time of the study design/scientific advice, the single arm study M13-982 would be sufficient on the assumption of a substantial increase in CR or of the rate of patients achieving MRD negativity would support the application, durability of responses and an acceptable safety profile.

The selection of response rate (ORR) as a primary endpoint seems acceptable in high-risk R/R CLL patients, provided responses are of reasonable durability and an acceptable safety profile. Prior to the introduction of BCRi, the prognosis for 17p del CLL patients has been poor due to the limited efficacy of immunotherapy and chemoimmunotherapy-based regimens. In the pivotal study M13-982, a subject was considered compliant if 80% of the assigned dose was taken over the course of the study, unless otherwise directed by the principal investigator. No subject was less than 80% compliant over the course of the study. Of the 107 subjects in the main cohort, 104 subjects achieved the target dose of 400 mg (3 subjects discontinued venetoclax prior to completing the lead-in period).

Efficacy data and additional analyses

Preliminary efficacy, pharmacokinetics, and overall safety in Study M12 -175 at doses from 150 to 1200 mg venetoclax for CLL/SLL subjects led to the selection of 400 mg as the dose to explore further in the CLL/SLL safety expansion cohort of this study. No MTD was reached or defined.

In the main cohort (107) subjects of the pivotal study M13-982, the majority were male (65.4%), white (97.2%) and ≥ 65 years of age (57.0%, median 67 years, range 37 to 85). The median number of prior therapies was 2 (range 1 – 10). All but one of the subjects had 17p deletion and the majority of subjects had additional high risk features of disease: 18.7% of subjects were ≥ 75 years of age; 81.1% (30 of 37) were IGVH unmutated; 37.4% (34 of 91) were refractory to fludarabine; 53.3% (57 of 107) had a lymph node > 5 cm; and 50.5% (54 of 107) had an ALC ≥ 25 × 10^9/L.

This study met its primary endpoint of ORR demonstrating that treatment of subjects with R/R CLL in the presence of 17p deletion with venetoclax 400 mg once daily resulted in a significantly higher ORR

than the null hypothesis of 40% (*P* value < 0.001). In original submission, the IRC assessed ORR was 79.4% in the total main cohort (n=107; investigator assessed ORR was 73.8%). The IRC assessed CR rate was 7.5% and the investigator assessed CR rate was 15.9%. There were 9 subjects assessed as CR by the investigator but assessed as PR by the IRC (7 due to residual target lymph node size > 1.5 cm, ranging from 1.6 to 3.4 cm).

Overall, differences in response assessments between the IRC and investigator were observed in 31 subjects. These differences showed no clear tendency of being more or less positive in either category but went in both directions and considering the rather complex procedure of response assessment, this seems expected and acceptable. Updated results with data cut-off 29 January 2016 show essentially similar results including confirmation of ORR in the SE cohort (n=51).

First response was observed at the first visit for most subjects in the main cohort with a median of 0.8 months, whereas achievement of CR/CRi took considerably longer with a median of ~8-10 months.

Progression-free survival at 12 months per investigator assessment was 75% in the main cohort and 80% in the SE cohort. Three subjects received a stem cell transplant after achieving best responses of CR, PR, and PR, respectively, by IRC assessment.

Survival data are still very immature with a total of 17 (15.9%) subjects who died in the main cohort. The Kaplan-Meier estimate of the proportion of subjects surviving at 12 months was 86.7% (30 April 2015).

MRD was an exploratory endpoint in study M13-982. No detectable MRD (sensitivity < 10^{-4}) was reported in the peripheral blood of 28 of 63 tested subjects. In the main cohort, MRD negativity in peripheral blood and on therapy was about 26%, i.e. higher than the complete remission rates. In most cases this is explained by residual lymph nodes slightly larger than accepted according to CR criteria. No obvious subgroup-related differences were reported.

With respect to subgroup analyses there are no conspicuous findings in reasonably large subgroups.

Patient-reported health related QoL measures were identified as exploratory efficacy endpoints for this study, including MDASI, EORTC QLQ-C30, EORTC QLQ-CLL16, EQ-5D-5L, and EQ VAS. The different measures of patient reported QoL generally indicated a mild to moderate improvement in the various dimensions and no net negative and significant changes were noted. However, results need to be interpreted with caution as they are observed exploratory endpoints in this single arm study.

Therefore, the above results from pivotal study M13-982 support efficacy of venetoclax in the first part of the indication:

> "Venclyxto monotherapy is indicated for the treatment of chronic lymphocytic leukaemia (CLL) in the presence of 17p deletion or *TP53* mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor".

The totality of data, including non-clinical data, shows that the activity of venetoclax is not influenced by del 17p/TP53 status. Prior failure on BCRi or CIT seems not to influence the efficacy of venetoclax to any major degree, however the number of patients in different subgroups is small. The reported results of study M14-032, in subjects who failed previous treatment with BCR-inhibitors the IRC assessed ORR was 30/43 after ibrutinib and 10/21 after idelalisib failure and corresponding PFS data at 6 months were 81% and 88%. In the update (10 June 2016) similar response rates (60-70%) were shown irrespective of del17p/TP53 status and prior therapy idelalisib or ibrutinib. Since the majority of patients without p17/TP53 mutation have received both prior chemoimmunotherapy and a BCRi this should be reflected in the indication as follows:

Venclyxto monotherapy is indicated for the treatment of CLL in the absence of 17p deletion or *TP53* mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor as the proportion of progression-free at 12 months was about 80% and median PFS was more than 2 years.

Additional efficacy data needed in the context of a conditional MA
Data on post-BCRi therapy are limited, therefore confirmation of efficacy is needed. This patient population is expected to increase as more CLL patients will (eventually) progress after BCRi treatment. A comparative clinical study in this setting is likely not to be feasible within an acceptable time frame considering that the BCRis have only been rather recently approved relative to the long PFS/DoR of these products as this is a requirement for a conditional approval. Sixty more patients are planned for enrolment in study M14-032; the extension of this supportive study will form the basis of additional efficacy data needed.

2.5.4. Conclusions on the clinical efficacy

In overall submitted studies showed a consistent efficacy in terms of ORR in both patient populations (with or without 17p del/ TP53 mutation) and demonstrate the activity of venetoclax. With a median exposure of around one year, efficacy of venetoclax monotherapy in the studied populations of R/R and high-risk (del17p) CLL seems unequivocal with ORR and PFS at 1 year of 75-80 %. Responses included CR in approximately 18%, overall efficacy appears consistent in relevant subgroups.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

In order to further confirm the efficacy of venetoclax in CLL patients who progressed on or after idelalisib or ibrutinib where patient numbers were low and because of the short follow up time the MAH should provide further data on safety and data on efficacy for study M14-032 of venetoclax in chronic lymphocytic leukaemia patients relapsed after or refractory to treatment with B-cell receptor signalling pathway inhibitor therapy.

2.6. Clinical 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. This safety population includes 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), as summarized below.

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

- Pivotal Study M13-982 in subjects with R/R or previously untreated CLL harboring the 17p del; 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)
- Supportive Study M14-032 in subjects with CLL that was R/R to ibrutinib or idelalisib treatment; N = 28 (400 mg dose)

The safety results from pivotal Study M13-982 in 17p del CLL subjects were largely similar to the safety results in Study M12-175 in R/R CLL (Arm A) and in Study M14 032 in BCRi failures, described further in individual clinical study reports (CSRs). Also, the safety results in the pooled dataset of all subjects who received 400 mg venetoclax in these 3 studies were largely similar to the individual study results. Thus, the safety evaluation of 400 mg QD venetoclax monotherapy is based on the pooled dataset of all subjects who received 400 mg venetoclax in the 3 monotherapy studies listed above (N = 289 subjects for all doses; N = 240 for the 400 mg dose).

The 3 ongoing venetoclax combination therapy studies listed below provide supportive safety data.

- Study M13-365 evaluated venetoclax + rituximab in subjects with relapsed CLL (N = 49) (Data cutoff date: 15 December 2014).
- Study GO28440 evaluated venetoclax + bendamustine/rituximab (BR) in subjects with R/R or previously untreated CLL (N = 19) (Data cutoff date: 28 November 2014).
- Study GP28331 evaluated venetoclax + obinutuzumab in subjects with R/R or previously untreated CLL (N = 20) (Data cutoff date: 28 November 2014).

One monotherapy substudy in subjects with NHL (Arm B of Study M12-175; N = 106) provides comparative data to help differentiate CLL-related AEs and risk factors from those attributable to venetoclax. It also provides supportive safety data with higher dose levels of venetoclax, as well as a food effect substudy.

A total of 6 completed clinical pharmacology studies, listed below, provide additional supportive safety data (N = 75 [includes 5 who did not receive venetoclax]):

The data from studies with combination therapy, monotherapy in NHL, and pharmacology studies are summarized separately and are not pooled.

All studies were conducted in accordance with International Conference on Harmonisation (ICH), Good Clinical Practice guidelines, and the ethical concepts of the Declaration of Helsinki.

In the response to the D120 LoI, a general safety update was provided for all subjects receiving 400 mg venetoclax (All 400 mg Analysis Set, N = 296). In addition, updated safety data for 17p del subjects receiving 400 mg venetoclax (N = 188) and subjects with previous BCRi failures receiving 400 mg venetoclax (N = 94) was also provided.

Patient exposure

Table 19: Updated analysis: Exposure to Venetoclax Monotherapy in R/R CLL (All 400 mg Analysis Set), 10 February 2016 data cut

	400 mg QD N = 296		
	All Subjects[a] n = 296	**17p Del[b] n = 188**	**BCRi Failure[c] n = 94**
Duration, n (%) of subjects			
> 60 to 104 weeks	91 (30.7)	65 (34.6)	6 (6.4)
> 104 weeks	28 (9.5)	15 (8.0)	0
Summary Statistics, months			
Mean (SD)	13.2 (8.36)	13.4 (7.85)	7.6 (4.49)
Median	11.4	11.9	7.8
Min – Max	0 – 43.7	0 – 30.1	0.1 – 20.8

BCRi = B-cell receptor inhibitor; QD = daily; SD = standard deviation; 17p del = 17p deletion

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 Arm A, and M14-032.

Note: Duration of exposure includes the dose ramp-up period during which subjects received venetoclax at dosages less than the target dose.

With the updated data cut the median follow-up for venetoclax increased by 1 month to 11.4 months (previously 10.3 months), with approximately 100 subjects who have received venetoclax for over 1 year. Longer exposure (up to 2 years) is available for at least 28 subjects.

In the 17p del group, close to 100 patients have been treated for 1 year. The safety profile is likely to be similar in the BCRi failure population and as the safety profiles are clearly different comparing BCRi:s and venetoclax making cross-intolerance a likely non-issue.

Adverse events

Table 20: Overview of Treatment-Emergent Adverse Events: R/R CLL (All 400 mg Analysis Set)

	400 mg QD N = 296		
Type of Adverse Event	**All Subjects[a] n = 296 n (%)**	**17p Del[b] n = 188 n (%)**	**BCRi Failure[c] n = 94 n (%)**
Any TEAE	293 (99.0)	185 (98.4)	94 (100.0)
Grade 3 or 4 TEAE	225 (76.0)	142 (75.5)	67 (71.3)
Serious TEAEs	144 (48.6)	95 (50.5)	46 (48.9)
TEAEs leading to			
Discontinuation of venetoclax[d]	27 (9.1)	20 (10.6)	7 (7.4)
Interruption of venetoclax	103 (34.8)	58 (30.9)	37 (39.4)
Reduced dose of venetoclax	35 (11.8)	24 (12.8)	8 (8.5)
Death	25 (8.4)	21 (11.2)	8 (8.5)
All deaths	53 (17.9)	43 (22.9)	17 (18.1)

BCRi = B-cell receptor inhibitor; QD = daily; TEAE = treatment-emergent adverse event; 17p del = 17p deletion

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 Arm A, and M14-032.

d. Events of malignant neoplasm progression were related to progression of the primary disease of CLL and are excluded.

Excluding disease progression, about 10% of patients discontinued venetoclax after median about 1 year of therapy indicating good tolerability in pre-treated CLL patients.

Common adverse events

Table 21: Treatment-Emergent Adverse Events Reported in ≥ 10% of Subjects (All 400 mg Analysis Set)

	400 mg QD N = 296		
System Organ Class Preferred Term (MedDRA v17.1)	**All Subjects[a] n = 296 n (%)**	**17p Del[b] n = 188 n (%)**	**BCRi Failure[c] n = 94 n (%)**
Any TEAE	248 (83.8)	159 (84.6)	69 (73.4)
Blood and lymphatic system disorders			
Anaemia	87 (29.4)	52 (27.7)	35 (37.2)
Neutropenia	120 (40.5)	75 (39.9)	33 (35.1)
Gastrointestinal disorders			
Constipation	43 (14.5)	22 (11.7)	11 (11.7)
Diarrhoea	115 (38.9)	71 (37.8)	33 (35.1)
Nausea	106 (35.8)	60 (31.9)	30 (31.9)
General disorders and administration site conditions			
Fatigue	77 (26.0)	44 (23.4)	26 (27.7)
Oedema peripheral	33 (11.1)	18 (9.6)	11 (11.7)
Pyrexia	46 (15.5)	30 (16.0)	8 (8.5)
Infections and infestations			
Upper respiratory tract infection	68 (23.0)	35 (18.6)	10 (10.6)
Investigations			
Neutrophil count decreased	33 (11.1)	11 (5.9)	21 (22.3)
Metabolism and nutrition disorders			
Hyperphosphataemia	43 (14.5)	22 (11.7)	16 (17.0)
Hypokalaemia	35 (11.8)	23 (12.2)	12 (12.8)
Musculoskeletal and connective tissue disorders			
Back pain	31 (10.5)	19 (10.1)	7 (7.4)
Nervous system disorders			
Headache	46 (15.5)	28 (14.9)	9 (9.6)
Respiratory, thoracic and mediastinal disorders			
Cough	48 (16.2)	26 (13.8)	17 (18.1)

BCRi = B-cell receptor inhibitor; QD = daily; TEAE = treatment-emergent adverse event; 17p del = 17p deletion

d. Subjects with R/R CLL in Studies M13-982, M12-175 Arm A, and M14-032.

Subjects with R/R CLL harboring 17p del; Studies M13-982, M12-175 Arm A, and M14-032.

Subjects with R/R CLL who previously failed BCRi therapy; Studies M13-982, M12-175 Arm A, and M14-032.

Treatment-Related Adverse Events (cut-off for original submission)

Adverse events with a reasonable possibility of being related to venetoclax that occurred in ≥ 10% of subjects in the All 400 mg Analysis Set were neutropenia (31.3%), nausea (23.3%), diarrhea (18.8%), fatigue (12.9%), hyperphosphatemia (11.3%), thrombocytopenia (10.4%), and anaemia (10.4%).

Tumour lysis syndrome was reported in a total of 17 subjects (5.9%). In the MAA module 2.7.4. Section 1.1.4.4, it is described that all TLS AESIs were medically reviewed and further categorized as

Clinical TLS (CTLS), Laboratory TLS (LTLS), or other reported TLS (i.e., did not meet criteria for either CTLS or LTLS) based on criteria published in the literature (Howard 2011).

Of the total of 5 cases of TLS recorded under the Current Amendment none fulfilled criteria for CTLS.

Grade 3/4 Adverse Events (updated)

Table 22: Treatment-Emergent Adverse Events NCI CTCAE Grade 3/4 Reported in ≥ 2% (All 400 mg Analysis Set)

	400 mg QD N = 296		
System Organ Class Preferred Term (MedDRA v17.1)	**All Subjects[a] n = 296 n (%)**	**17p Del[b] n = 188 n (%)**	**BCRi Failure[c] n = 94 n (%)**
Any TEAE grade 3 or 4	225 (76.0)	142 (75.5)	67 (71.3)
Blood and lymphatic system disorders			
Anaemia	45 (15.2)	27 (14.4)	18 (19.1)
Autoimmune haemolytic anaemia	13 (4.4)	12 (6.4)	1 (1.1)
Febrile neutropenia	17 (5.7)	9 (4.8)	10 (10.6)
Immune thrombocytopenic purpura	6 (2.0)	5 (2.7)	1 (1.1)
Leukopenia	10 (3.4)	7 (3.7)	1 (1.1)
Neutropenia	110 (37.2)	69 (36.7)	29 (30.9)
Thrombocytopenia	40 (13.5)	29 (15.4)	14 (14.9)
Gastrointestinal disorders			
Abdominal pain	6 (2.0)	3 (1.6)	2 (2.1)
Diarrhoea	4 (1.4)	3 (1.6)	3 (3.2)
General disorders and administration site conditions			
Fatigue	6 (2.0)	0	3 (3.2)
Infections and infestations			
Pneumonia	15 (5.1)	9 (4.8)	7 (7.4)

Table 23: Treatment-Emergent Adverse Events NCI CTCAE Grade 3/4 Reported in ≥ 2% (All 400 mg Analysis Set) (Continued)

	400 mg QD N = 296		
System Organ Class Preferred Term (MedDRA v17.1)	**All Subjects[a] n = 296 n (%)**	**17p Del[b] n = 188 n (%)**	**BCRi Failure[c] n = 94 n (%)**
Investigations			
Blood lactate dehydrogenase increased	6 (2.0)	4 (2.1)	2 (2.1)
Lymphocyte count decreased	9 (3.0)	3 (1.6)	4 (4.3)
Neutrophil count decreased	26 (8.8)	9 (4.8)	16 (17.0)
Platelet count decreased	11 (3.7)	4 (2.1)	8 (8.5)
White blood cell count decreased	11 (3.7)	3 (1.6)	10 (10.6)
Metabolism and nutrition disorders			
Hyperglycaemia	10 (3.4)	3 (1.6)	5 (5.3)
Hypocalcaemia	6 (2.0)	3 (1.6)	3 (3.2)
Hypokalaemia	10 (3.4)	8 (4.3)	4 (4.3)
Hypophosphataemia	14 (4.7)	9 (4.8)	7 (7.4)
Tumour lysis syndrome	10 (3.4)	8 (4.3)	3 (3.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression	6 (2.0)	6 (3.2)	0
Squamous cell carcinoma of skin	9 (3.0)	2 (1.1)	1 (1.1)
Vascular disorders			
Hypertension	7 (2.4)	4 (2.1)	1 (1.1)

BCRi = B-cell receptor inhibitor; QD = daily; TEAE = treatment-emergent adverse event; 17p del = 17p deletion

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 Arm A, and M14-032.

Hyperglycaemia grade3/4 and hypertension grade 3/4 were reported in 10 and 9 subjects. More information is requested.

Adverse Events Over Time

Adverse events were evaluated by the first onset and by prevalence over time. In general, TEAEs had the highest incidence and prevalence during initiation of therapy (Days 1-90).

A graphical illustration of the incidence and prevalence of the most frequent TEAEs was provided. Apart from second primary tumour, the incidence of all other AE.s was highest the first month (similar first and second month for "autoimmune events"). Note that there were no new hepatic events after month 2, whilst the prevalence appears to stay stable at 1.2% after month 3. The prevalence of grade 1-2 infections is rather stable over time whilst grade 3-4 events gradually decreases as does the incidence. All this is essentially as expected.

Other Significant Adverse Events and AESI

Tumour lysis syndrome (updated cut-off)

Tumour lysis syndrome (TLS), resulting from the on target pharmacologic effect of venetoclax, was identified as a risk early in the first-in-human Study M12-175 based on significant reductions in absolute lymphocyte count (ALC) and responses in lymph nodes within the first 4 to 24 hours of dosing. Significant findings and adjustments to the clinical program regarding prevention of TLS is extensively described in module 2.7.4 (Section 2.1.5.1) and include ramp-up dosing and TLS prevention.

Since May 2014, a total of 122 subjects have received venetoclax following the Current Amendment, which aligns the prophylactic measures with the patients' relative risk. Adverse events of TLS were reported in 4 (3.3%) subjects (table below).

Table 24: Tumour Lysis Syndrome TEAEs with Current Prophylactic/Management Measures in CLL

	Current Amendment (May 2014 – Feb 2016)	
TEAE	**All N = 122**	**17p Del N = 68**
All TLS AESI[a]	4 (3.3)	3 (4.4)
NCI CTCAE Grade ≥ 3 TLS AESI	4 (3.3)	3 (4.4)
Serious TLS AESI	3 (2.5)	3 (4.4)
TLS AESI led to		
Discontinuation of venetoclax	0	0
Interruption of venetoclax	4 (3.3)	3 (4.4)
Reduced dose of venetoclax	0	0
Death	0	0

AESI = adverse events of special interest; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; TEAE = treatment-emergent adverse event; TLS = tumour lysis syndrome; 17p del = 17p deletion

a. TEAE with preferred term in the SMQ of tumour lysis syndrome (narrow).

Since metabolic abnormalities precede TLS, all adverse events for relevant metabolic events were reviewed (i.e., hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia) with focus on the Current Amendment Analysis Set (table below).

Table 25: Laboratory TEAEs Relevant to TLS: Venetoclax in R/R CLL (Current Amendment Analysis Set)

	Number (%) of Subjects[a]							
	Hyperuricemia[b]		Hyperkalaemia[b]		Hyperphosphataemia[b]		Hypocalcaemia[b]	
	All N = 122	17p Del N = 68	All N = 122	17p Del N = 68	All N = 122	17p Del N = 68	All N = 122	17p Del N = 68
Any adverse event	10 (8.2)	5 (7.4)	19 (15.6)	11 (16.2)	18 (14.8)	4 (5.9)	12 (9.8)	4 (5.9)
NCI CTCAE Grade ≥ 3	1 (0.8)	0	1 (0.8)	0	3 (2.5)	1 (1.5)	2 (1.6)	0
Serious adverse event	0	0	4 (3.3)	3 (4.4)	1 (0.8)	0	0	0
AE led to								
Discontinuation of venetoclax	0	0	0	0	0	0	0	0
Interruption of venetoclax	0	0	3 (2.5)	1 (1.5)	3 (2.5)	0	0	0
Reduced dose of venetoclax	0	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; R/R = relapsed or refractory; TEAE = treatment emergent adverse event; 17p del = 17p deletion

a. Subjects with R/R CLL in Studies M13-982 (safety expansion cohort) and M14-032 (initial venetoclax dosage of 20 mg QD for 1 week). All subjects were in the 400 mg dose group. (Current TLS Measures Analysis Set).

b. Data for preferred terms were combined as follows:

Hyperuricemia: preferred terms of hyperuricaemia and blood uric acid increased

Hyperkalemia: preferred terms of hyperkalaemia and blood potassium increased

Hyperphosphatemia: preferred terms of hyperphosphataemia and blood phosphorus increased

Hypocalcemia: preferred terms of hypocalcaemia and blood calcium decreased

The risk for TLS is considerably reduced by the installed prophylactic measures, but TLS grade 3 does occur at an incidence of about 3%.

Neutropenia (updated cut-off)

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.

All neutropenia AESIs reported in the All 400 mg Analysis Set are summarized in the table below; neutropenia AESIs were reported in 148/296 (50.0%) of subjects, and the reported preferred terms were neutropenia, neutrophil count decreased, and febrile neutropenia. Several subjects had pre-existing neutropenia prior to entering the study.

Table 26: Neutropenia AESIs (All 400 mg Analysis Set)

TEAE (MedDRA v17.1)	400 mg QD N = 296 All Subjects[a] n = 296 n (%)	17p Del[b] n = 188 n (%)	BCRi Failure[c] n = 94 n (%)
All Neutropenia AESIs[d]	148 (50.0)	87 (46.3)	52 (55.3)
by Preferred Term			
Neutropenia	120 (40.5)	75 (39.9)	33 (35.1)
Neutrophil count decreased	33 (11.1)	11 (5.9)	21 (22.3)
Febrile neutropenia	17 (5.7)	9 (4.8)	10 (10.6)
NCI CTCAE Grade ≥ 3 AESI	131 (44.3)	79 (42.0)	43 (45.7)
Serious AESI	20 (6.8)	12 (6.4)	9 (9.6)
AESI led to			
Discontinuation of venetoclax	1 (0.3)	0	0
Interruption of venetoclax	22 (7.4)	12 (6.4)	10 (10.6)
Reduced dose of venetoclax	18 (6.1)	14 (7.4)	3 (3.2)
Death	0	0	0

AESI = adverse events of special interest; BCRi = B-cell receptor inhibitor; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; QD = daily; TEAE = treatment-emergent adverse event; 17p del = 17p deletion

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 Arm A, and M14-032.
d. Includes preferred terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection, and neutropenic sepsis.

[In 106 NHL patients included in study M12-175 Arm B, grade ≥3 neutropenia occurred in ~10%].

Neutropenia was found not to be dose-limiting based on exposure-safety analysis. Still, among the dose escalation cohorts of study M12-175, neutropenia was observed in 41.7% (25/60) of subjects in 400 mg safety expansion cohort and ≥ 57.1% of subjects in dose cohorts of 600 mg or higher. Laboratory data combined with the exposure-response analyses suggest that if venetoclax contributes to neutropenia clinically, it is not dose-dependent across the range of doses that demonstrate clinical efficacy (i.e., 150 to 1200 mg).

Serious infection AESI (updated cut-off)

Adverse events in the infections and infestations System Organ Class (SOC) that were reported in the All 400 mg Analysis Set are summarized in the table below; infections Grade ≥ 3 were reported in 59 (19.9%) of subjects.

Table 27: Infections and Infestation SOC AESIs

TEAE (MedDRA v17.1)	400 mg QD N = 296		
	All Subjects[a] n = 296 n (%)	17p Del[b] n = 188 n (%)	BCRi Failure[c] n = 94 n (%)
NCI CTCAE Grade ≥ 3 AESI	59 (19.9)	38 (20.2)	25 (26.6)
Serious AESI	61 (20.6)	39 (20.7)	24 (25.5)
AESI led to			
Discontinuation of venetoclax	2 (0.7)	1 (0.5)	1 (1.1)
Interruption of venetoclax	30 (10.1)	16 (8.5)	13 (13.8)
Reduced dose of venetoclax	8 (2.7)	6 (3.2)	2 (2.1)
Death	4 (1.4)	3 (1.6)	2 (2.1)

AESI = adverse event of special interest; BCRi = B-cell receptor inhibitor; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; SOC = system organ class; TEAE = treatment-emergent adverse event; 17p del = 17p deletion

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 Arm A, and M14-032.

In the original submission, the most common preferred terms among infection SAEs were pneumonia (5.0%) and upper respiratory tract infection (1.3%).

For comparison, infection AESIs in the NHL population were reported in only 36% (38/106) of subjects, with grade ≥ 3 events in 10% (11/106) of subjects, and serious events in 10% (11/106) of subjects.

Serious infection is included as an important potential risk in the RMP.

The search for opportunistic infections was comprehensive and 5 serious events were identified in 4 individuals. All subjects were previously treated with fludarabine. One subject had grade3 neutropenia, but this was a case of disseminated herpes (with a history of zoster). There were three cases of pneumocystis and one of pulmonary aspergillosis, thereof one with grade 1-2 neutropenia. Events were diagnosed (TTO) day 67 to 672. Event rates and distribution of opportunistic infections are inconspicuous, but obviously it cannot be excluded that treatment with venetoclax contributed, but the signal is considered weak and prior fludarabine therapy and the underlying condition are more likely to be causative.

Second Primary Malignancy

Due to underlying immune impairment, patients with CLL are at an increased risk of second malignancies, defined as a new primary cancer in a subject with a history of cancer (Dasanu 2007, Streu 2014).

No signal related to second primary malignancies was identified at the time of the MAA submission, Additional data, including data on a total of 296 subjects in the All 400 mg Analysis Set, which included 188 subjects with 17p deletion, were submitted; long-term data for up to 43.7 months (median exposure 11.4 months), with 100 subjects with at least 1 year of follow-up and 28 subjects with at least 2 years of follow-up.

Table 28: Second Primary Malignancy AESIs: R/R CLL (Venetoclax Monotherapy)

	Number (%) of Subjects				
	Venetoclax 400 mg QD		Venetoclax Any Dose		
TEAE (MedDRA v17.1)	All[a] N = 296	17p Del[b] N = 188	All[a] N = 345	17p Del[b] N = 205	BCRi Failure[c] N = 94
All second primary malignancy AESIs[d]	39 (13.2)	17 (9.0)	49 (14.2)	23 (11.2)	6 (6.4)
By preferred term for non-melanoma skin cancers					
Squamous cell carcinoma of skin	17 (5.7)	6 (3.2)	21 (6.1)	8 (3.9)	1 (1.1)
Basal cell carcinoma	9 (3.0)	3 (1.6)	11 (3.2)	5 (2.4)	1 (1.1)
By preferred term for all other cancers					
Squamous cell carcinoma	4 (1.4)	2 (1.1)	4 (1.2)	2 (1.0)	1 (1.1)
Breast cancer	2 (0.7)	2 (1.1)	2 (0.6)	2 (1.0)	0
Prostate cancer	2 (0.7)	0	3 (0.9)	0	1 (1.1)
Squamous cell carcinoma of lung	1 (0.3)	0	2 (0.6)	0	1 (1.1)
Adenocarcinoma of colon	1 (0.3)	1 (0.5)	1 (0.3)	1 (0.5)	0
Bladder transitional cell carcinoma recurrent	0	0	1 (0.3)	0	0
Bronchial carcinoma	1 (0.3)	1 (0.5)	1 (0.3)	1 (0.5)	0
Hodgkin's disease	1 (0.3)	1 (0.5)	1 (0.3)	1 (0.5)	0
Keratoacanthoma	1 (0.3)	0	1 (0.3)	0	0
Laryngeal squamous cell carcinoma	0	0	1 (0.3)	0	0
Lung adenocarcinoma	1 (0.3)	0	1 (0.3)	0	0
Malignant melanoma	1 (0.3)	0	1 (0.3)	0	0
Malignant neoplasm of unknown primary site	1 (0.3)	1 (0.5)	1 (0.3)	1 (0.5)	0
Mucoepidermoid carcinoma	1 (0.3)	0	1 (0.3)	0	1 (1.1)
Myelodysplastic syndrome	1 (0.3)	1 (0.5)	1 (0.3)	1 (0.5)	0
Neuroendocrine carcinoma	1 (0.3)	1 (0.5)	1 (0.3)	1 (0.5)	0
Nodal marginal zone B-cell lymphoma	0	0	1 (0.3)	1 (0.5)	0
Oesophageal squamous cell carcinoma	0	0	1 (0.3)	1 (0.5)	0
Papillary thyroid cancer	1 (0.3)	0	1 (0.3)	0	0
Plasma cell myeloma	1 (0.3)	1 (0.5)	1 (0.3)	1 (0.5)	1 (1.1)
Skin cancer	1 (0.3)	0	1 (0.3)	0	0

Table 29: Second Primary Malignancy AESIs: R/R CLL (Venetoclax Monotherapy) (Continued)

	Number (%) of Subjects				
	Venetoclax 400 mg QD		Venetoclax Any Dose		
TEAE (MedDRA v17.1)	All[a] N = 296	17p Del[b] N = 188	All[a] N = 345	17p Del[b] N = 205	BCRi Failure[c] N = 94
NCI CTCAE[e] grade ≥ 3 AESI	25 (8.4)	11 (5.9)	31 (9.0)	14 (6.8)	5 (5.3)
Death	1 (0.3)	1 (0.5)	1 (0.3)	1 (0.5)	1 (1.1)

Autoimmune events

Autoimmunity is of common occurrence in the CLL population. In the All Doses Analysis Set, autoimmune hemolytic anaemia (AIHA) occurred in 4.5% (13/289) of subjects and immune thrombocytopenic purpura (ITP) occurred in 3.5% (10/289) of subjects, whereas the incidence in NHL subjects (Arm B of Study M12-175) was 0.9% (1/106) for AIHA and 0% (0/106) for ITP.

Autoimmune hemolytic anaemia was reported in 5.4% (13/240) of subjects in the All 400 mg Analysis Set, and the events were grade 3 (n = 7) or 4 (n = 3) for the majority of these subjects; 2.9% (7/240) of subjects experienced serious events. The events of AIHA led to venetoclax dose interruption in 3 subjects, venetoclax dose reduction in 1 subject, and venetoclax discontinuation in 2 subjects.

Immune thrombocytopenic purpura was reported in 2.9% (7/240) of subjects in the All 400 mg Analysis Set, and the events were grade 3 (n = 1) or 4 (n = 5) for the majority of these subjects (6/7); 0.8% (2/240) of subjects experienced serious events. The events of ITP led to venetoclax dose interruption in 4 subjects and venetoclax dose reduction in 1 subject. No events led to venetoclax discontinuation.

Autoimmune events encountered in CLL comprise a wide spectrum of diagnoses, some of which may also precede the CLL diagnosis. A broad search for autoimmune events and co-morbidities (including non-haematological events and pre-existing conditions) was performed. Reported events are those expected in CLL and there were, e.g. no reported events of thyroid disorders, events typically seen in cases of autoimmunity related to therapy.

Transformation/Richter's Syndrome

Of the 289 subjects in the R/R CLL All Doses Analysis Set, 29 subjects were discontinued because of progression of disease that included Richter's syndrome: 15 in Study M12-175, 13 in Study M13-982, and 1 in Study M14-032.

The possibility of ongoing transformation to Richter's syndrome prior to initiating venetoclax cannot be ruled out in 13 of the 29 subjects where Richter's syndrome was reported within 6 months of initiating venetoclax therapy. In general, the majority of the subjects had multiple risk factors (e.g., R/R disease, 17p del, multiple prior cytotoxic therapies, prior fludarabine-based therapy). Updated data on Richter's transformation further reveal that among the 345 subjects with CLL treated with any dose of venetoclax monotherapy and included in the updated safety analyses, 37 cases were identified to have RT in course of CLL disease progression. The current incidence of RT in studies with venetoclax monotherapy is 10.7%; the incidence of RT among non-responders (20.7%) was higher than among subjects with documented clinical response by investigator (6.9%). The mean onset of RT from

venetoclax initiation was 290.5 (range: 9 – 700) days, with 14 subjects diagnosed with RT within 6 months after first dose of venetoclax.

Gastrointestinal Disorders (SOC)

Diarrhea occurred in 35.4% (85/240) of subjects in the All 400 mg Analysis Set (however, grade 3 AEs occurred in only 2 subjects and no grade 4 events were reported. The majority of diarrhoea AEs were manageable with no treatment or with standard medical care. Few subjects required a dose reduction (n = 2) or dose interruption (n = 3) of venetoclax. Diarrhoea was serious in 1 subject. Only 1 subject discontinued venetoclax because of diarrhoea (Subject 134 due to grade 2 diarrhoea and vomiting).

Nausea occurred in 33.3% (80/240) of subjects and vomiting occurred in 14.6% (35/240) subjects in the All 400 mg Analysis Set, however, grade 3 AEs occurred in only 2 subjects each and no grade 4 events were reported. The majority of nausea and vomiting AEs were manageable with no treatment or standard medical care. Serious AEs were reported in 1 subject for vomiting. Only 1 subject discontinued venetoclax because of these events (Subject 134 due to grade 2 diarrhoea and vomiting).

The prevalence of diarrhoea decreased from 25.4% (61/240) during the first 90 days of venetoclax treatment to approximately 10% – 14% during subsequent 90-day intervals. For nausea, the prevalence decreased from 26.3% during the first 90 days of treatment to approximately 14% – 17% during subsequent 90-day intervals. For vomiting, the prevalence decreased from 10.0% during the first 90 days of treatment to approximately 2% to 5% during subsequent 90-day intervals.

Two subjects in the All 400 mg Analysis Set had SAEs of small intestinal obstruction that was fatal for one subject, and resolved within 4 days for the other subject. The investigator indicated alternative etiologies of umbilical hernia for the fatal case and diffuse large B-cell lymphoma (DLBCL) for the resolved case.

Hence, gastrointestinal events were largely of grade ≤2 and gradually became less frequent during treatment. Tolerance may be different in individuals with pre-existing gastrointestinal conditions eg IBD.

Cardiac Disorders (SOC)

Consistent with the age of the study population (median of 66 years), 60.8% of subjects in the All 400 mg Analysis Set had medical histories of diseases or conditions reported in the cardiovascular system prior to starting venetoclax. A total of 8 subjects in the All 400 mg Analysis Set experienced SAEs in the cardiac disorders SOC, including cardiopulmonary failure for 1 subject. The cardiopulmonary failure occurred 7 days after the last dose of venetoclax and was fatal. The SAEs for the remaining 7 subjects were assessed by the investigator as grade 2 or 3 and none resulted in venetoclax discontinuation or dose reduction. All SAEs were assessed by the investigator as having no reasonable possibility of being related to venetoclax.

In the All 400 mg Analysis Set, TEAEs of atrial fibrillation or atrial flutter were reported in a total of 10 subjects: 9/240 for atrial fibrillation and 1/240 for atrial flutter. Nine of the 10 subjects were ≥ 65 years of age (range: 64 to 78 years). Three of the 4 atrial fibrillation SAEs were transient and resolved. For the remaining SAE of atrial fibrillation, the investigator attributed this event to the subject having to stop taking amiodarone to participate in the study. The SAE of atrial flutter was ongoing as of the data cutoff date.

No cases of torsade de pointes were identified. A total of 7 subjects had TEAEs reported in the SMQ of torsade de pointes/QTc prolongation: sudden death in 1 subject and syncope in 6 subjects. The

sudden death was in the setting of tumour lysis syndrome. All 6 subjects with syncope had other plausible reasons for syncope unrelated to prolonged QT interval.

Overall, the number and scope of cardiac events (including atrial fibrillation) recorded in the venetoclax studies appear to be within the expected range for the study population. Further it was clarified that there were eight cardiac events in in 111 subjects without known history of cardiac disorders and the events were diverse; 1 case of tachycardia and 1 case of palpitation in subjects below 60 years of age.

Bleeding Adverse Events (Haemorrhages SMQ)

Adverse events in the haemorrhages SMQ (narrow search) were reported in 13.8% (33/240) of subjects in the All 400 mg Analysis Set and the events were grade 3 (n = 5) or 4 (n = 4) for 9 subjects. These events were serious in 6 subjects, all considered to have no reasonable possible relationship to venetoclax by the investigator. The events in the haemorrhages SMQ led to venetoclax dose interruption in 4 subjects, venetoclax dose reduction in 1 subject, and venetoclax discontinuation in 1 subject.

A total of 42% (101/240) subjects in the All 400 mg Analysis Set were receiving anticoagulant and/or antiplatelet medications (except warfarin which was exclusionary).

Of the 9 subjects with grade ≥ 3 events, 6 subjects had ITP. Of the 6 subjects with ITP, only 1 subject with grade 4 ITP had a concurrent grade 2 AE of bleeding diathesis; both events were assessed by investigator as having no reasonable possibility of being related to venetoclax. The grade ≥3 events for the remaining 3 subjects (3/240) were all considered to have no reasonable possible relationship to venetoclax by the investigator (1 event of fatal haemorrhagic stroke concurrent with serious deep vein thrombosis (DVT), 1 gastric ulcer haemorrhage attributed to massive infiltration of gastric mucosa by aggressive lymphoma (Richter's transformation), and 1 upper gastrointestinal haemorrhage in setting of reflex esophagitis).

The incidence of AEs in the hemorrhage SMQ (narrow search) in the All 400 mg Analysis Set was comparable among subjects on concurrent anticoagulant and/or antiplatelet medications (16.8% [17/101]) compared with subjects not on concurrent anticoagulants (11.5% [16/139]).

Overall, the incidence of haemorrhage appears to be within the expected range for a similar population. A somewhat higher incidence in subjects with ITP and concomitant anticoagulant therapy would also be expected.

Hepatobiliary Disorders (SOC) and DILI

Adverse events in the hepatobiliary disorders SOC occurred in 4.2% (10/240) of subjects in the All 400 mg Analysis Set, and the events were grade 1 or 2 for the majority of these subjects (6/10). There was one SAE of hepatic function abnormal in one Study M13-982. This SAE was fatal and occurred in an 85-year-old male subject with history of prostate cancer and pre-existing elevations in LFT parameters. This event was considered to have no reasonable possibility of being related to venetoclax.

A medical review of all subjects with events retrieved using the drug-related hepatic disorders SMQ (narrow) in the All 400 mg Analysis Set did not identify any subject meeting Hy's law.

One case reported under the preferred term of DILI was reported in Study GO27878. This study is a study in B-cell NHL and DLBCL (ongoing and not included in this Summary of Clinical Safety). The subject was taking concomitant duloxetine for depression. The subject had a negative response to dechallenge and other possible etiological factors were present according to the investigator.

The reported cases of hepatobiliary disorders or suspected DILI were either mild or observed in contexts with other possible aetiological factors present (progressive disease, multiorgan failure with or without TLS, or other therapeutic agents). It was further clarified that there were altogether 2 cases of possible DILI in the full studies program (in about 1500), one case each in DLBC and AML. Due to concomitant treatment causality in relation to venetoclax can hardly be properly assessed.

Deaths (original cut-off) and other Serious adverse events (updated cut-off)

A total of 7 deaths, out of the 18 deaths in the All 400 mg Analysis Set (N = 240), had causes other than disease progression, as assessed by the investigator. Upon medical review, they were consistent with the elderly patient population with multiple risk factors including advanced CLL, and were all considered by the investigator to have no reasonable possibility of being related or probably not related to study drug (see table above).

Three additional deaths were reported in other dose groups, and 1 of these deaths had a cause other than disease progression. Therefore, across all 289 subjects included in the R/R CLL pooled analysis sets, there were 8 deaths (out of the 21 total deaths reported from TEAEs) that had causes other than disease progression.

Deaths in Other Supportive Studies

In the venetoclax combination therapy studies in R/R CLL (Studies M13-365, GO28440, and GP28331), a total of 2 fatal TEAEs were reported, both in Study M13-365 (one subject due to malignant neoplasm progression and one subject due to hyperkalaemia in the setting of TLS).

A total of 8 fatal TEAEs were reported in subjects with NHL who received venetoclax monotherapy in Study M12-175 (Arm B): malignant neoplasm progression for 7 subjects and respiratory failure (with alternative etiology of mantle cell lymphoma) for 1 subject.

No deaths were reported in the Phase 1 clinical pharmacology studies.

Other Serious Adverse Events (updated cutoff)

Table 30: Serious TEAEs Reported in ≥ 2 Subjects (All 400 mg Analysis Set)

	400 mg QD N = 296		
System Organ Class Preferred Term (MedDRA v17.1)	**All Subjects[a] n = 296 n (%)**	**17p Del[b] n = 188 n (%)**	**BCRi Failure[c] n = 94 n (%)**
Any SAE	144 (48.6)	95 (50.5)	46 (48.9)
Blood and lymphatic system disorders			
Anaemia	5 (1.7)	3 (1.6)	1 (1.1)
Autoimmune haemolytic anaemia	9 (3.0)	8 (4.3)	1 (1.1)
Febrile neutropenia	15 (5.1)	8 (4.3)	8 (8.5)
Immune thrombocytopenic purpura	2 (0.7)	1 (0.5)	1 (1.1)
Lymphadenopathy	2 (0.7)	2 (1.1)	0
Neutropenia	5 (1.7)	4 (2.1)	1 (1.1)
Thrombocytopenia	6 (2.0)	5 (2.7)	2 (2.1)
Cardiac disorders			
Angina pectoris	3 (1.0)	3 (1.6)	0
Atrial fibrillation	5 (1.7)	3 (1.6)	0
Gastrointestinal disorders			
Abdominal pain	2 (0.7)	2 (1.1)	0
Abdominal pain upper	2 (0.7)	2 (1.1)	0
Ascites	2 (0.7)	2 (1.1)	1 (1.1)
Small intestinal obstruction	3 (1.0)	1 (0.5)	1 (1.1)
Vomiting	2 (0.7)	2 (1.1)	0
General disorders and administration site conditions			
General health deterioration	2 (0.7)	2 (1.1)	0
Influenza like illness	2 (0.7)	2 (1.1)	0
Multi-organ failure	3 (1.0)	2 (1.1)	3 (3.2)
Pyrexia	9 (3.0)	8 (4.3)	0

Table 31: Serious TEAEs Reported in ≥ 2 Subjects (All 400 mg Analysis Set) (Continued)

	400 mg QD N = 296		
System Organ Class Preferred Term (MedDRA v17.1)	**All Subjects[a] n = 296 n (%)**	**17p Del[b] n = 188 n (%)**	**BCRi Failure[c] n = 94 n (%)**
Infections and infestations			
Cellulitis	3 (1.0)	2 (1.1)	1 (1.1)
Herpes Zoster	2 (0.7)	2 (1.1)	0
Lower respiratory tract infection	2 (0.7)	2 (1.1)	0
Pneumocystis jirovecii pneumonia	2 (0.7)	2 (1.1)	0
Pneumonia	16 (5.4)	11 (5.9)	6 (6.4)
Pneumonia bacterial	2 (0.7)	0	1 (1.1)
Septic shock	3 (1.0)	2 (1.1)	2 (2.1)
Staphylococcal bacteraemia	2 (0.7)	0	1 (1.1)
Upper respiratory tract infection	5 (1.7)	3 (1.6)	0
Urinary tract infection	3 (1.0)	2 (1.1)	2 (2.1)
Urosepsis	2 (0.7)	2 (1.1)	0
Investigations			
Blood creatinine increased	2 (0.7)	2 (1.1)	1 (1.1)
Blood potassium increased	2 (0.7)	1 (0.5)	2 (2.1)
Metabolism and nutrition disorders			
Fluid overload	3 (1.0)	1 (0.5)	1 (1.1)
Hypercalcaemia	3 (1.0)	3 (1.6)	2 (2.1)
Hyperkalaemia	2 (0.7)	2 (1.1)	1 (1.1)
Hyperphosphataemia	2 (0.7)	1 (0.5)	1 (1.1)
Musculoskeletal and connective tissue disorders			
Neck pain	2 (0.7)	2 (1.1)	1 (1.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer	2 (0.7)	2 (1.1)	0
Malignant neoplasm progression	18 (6.1)	17 (9.0)	2 (2.1)
Prostate cancer	2 (0.7)	0	1 (1.1)
Squamous cell carcinoma	2 (0.7)	2 (1.1)	0

Table 32: Serious TEAEs Reported in ≥ 2 Subjects (All 400 mg Analysis Set) (Continued)

	400 mg QD N = 296		
System Organ Class Preferred Term (MedDRA v17.1)	**All Subjects[a] n = 296 n (%)**	**17p Del[b] n = 188 n (%)**	**BCRi Failure[c] n = 94 n (%)**
Nervous system disorders			
Cerebrovascular accident	2 (0.7)	2 (1.1)	1 (1.1)
Syncope	2 (0.7)	2 (1.1)	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	3 (1.0)	2 (1.1)	1 (1.1)
Vascular disorders			
Deep vein thrombosis	2 (0.7)	2 (1.1)	0

BCRi = B-cell receptor inhibitor; QD = daily; TEAE = treatment-emergent adverse event; 17p del = 17p deletion

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 Arm A, and M14-032.

The most common serious TEAEs were malignant neoplasm progression (6.1%), pneumonia (5.4%), and febrile neutropenia (5.1%). All malignant neoplasm progression events were related to progression of the primary disease of CLL/SLL.

Laboratory findings

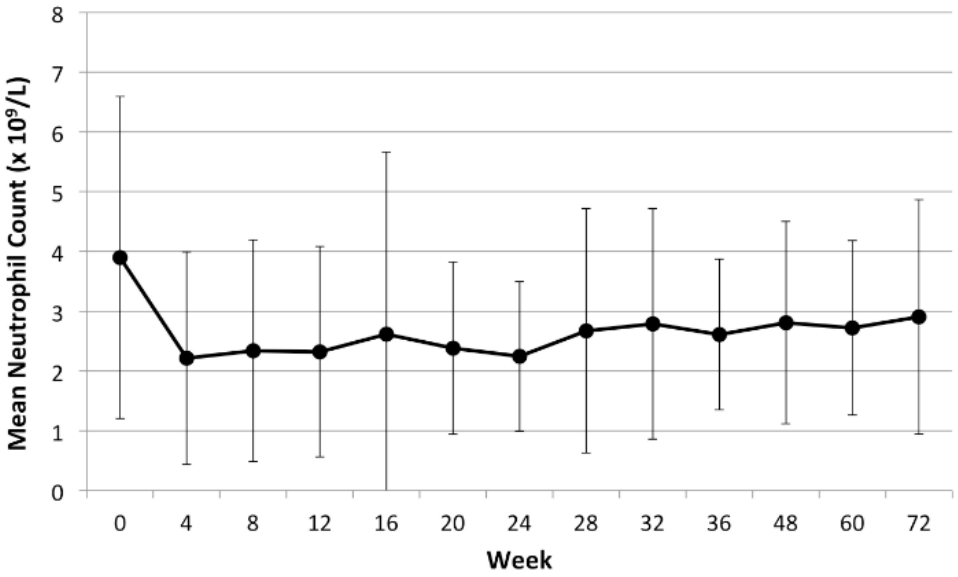
Haematology

Shifts of haematology parameters to grade 3/4 were frequently seen but generally seem to have abated at last/final visit.

Neutropenia Decreases Over Time

The risk of neutropenia with venetoclax treatment decreases over time, as observed in the All 400 mg Analysis set. Clinical laboratory results for mean neutrophil counts over time showed a decrease from 3.9×10^9/L at baseline to 2.2×10^9/L at Week 4, and then partially recovered, stabilizing between 2.6 and 2.9×10^9/L from Week 28 throughout the study as shown in Figure 16 here below.

Figure 16: Mean (± SD) Neutrophil Count Over Time: Monotherapy R/R CLL (All 400 mg Analysis Set)

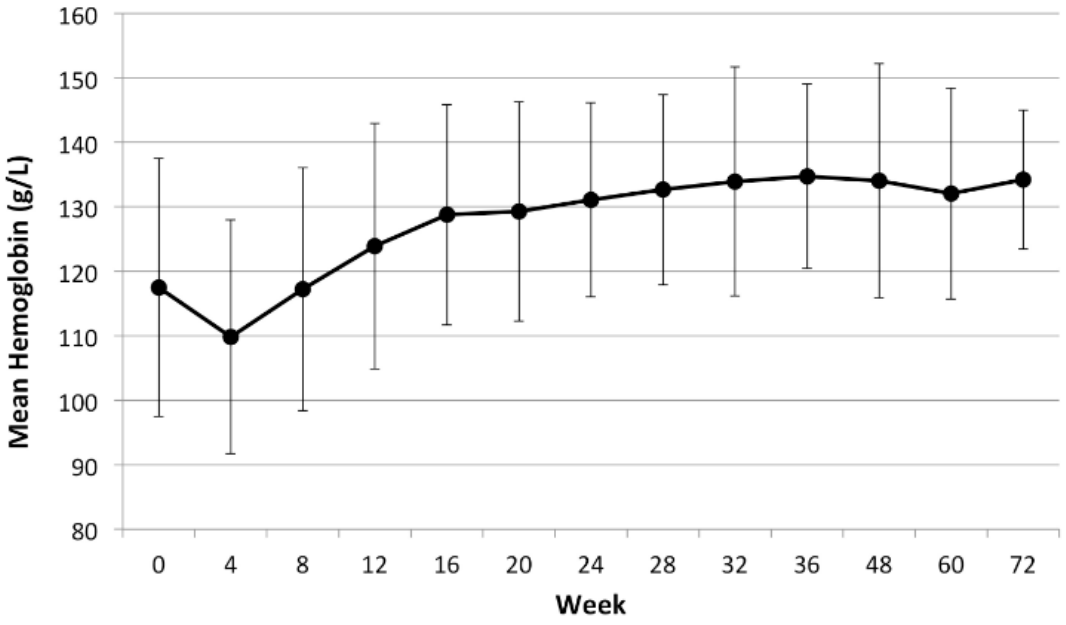


Mean ANC-values appear more or less stationary following an initial decrease at week 4. This is despite the use of G-CSF in a significant proportion of subjects (eg 21.2% for Days 91 – 180).

Anaemia and haemoglobin decreased

The first onset of anaemia (or haemoglobin decreased) AEs was greatest during the first 90 days of venetoclax treatment (26.7% of subjects, which represents 64 of the 70 subjects with events), and decreased to 1.4% during the next 90 days and was no more than 3% for each 90-day interval thereafter. Similarly, the prevalence of anaemia (or related preferred terms) was greatest during the first 90 days of treatment and decreased during each 90-day interval thereafter.

Figure 17: Mean (± SD) Haemoglobin Value Over Time: Monotherapy R/R CLL (All 400 mg Analysis Set)



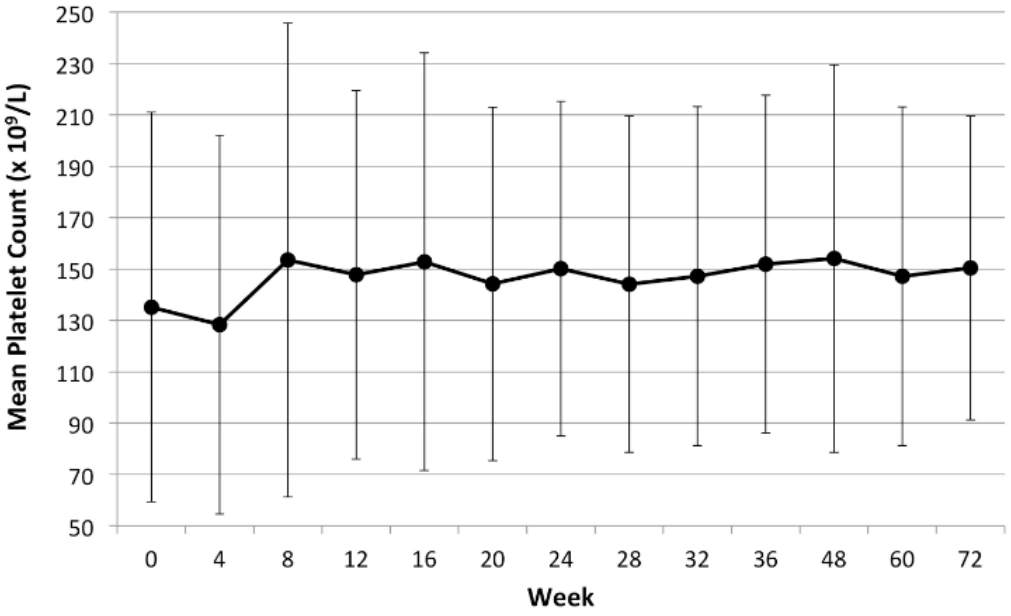
CLL = chronic lymphocytic leukaemia; R/R = relapsed or refractory; SD = standard deviation

The mean haemoglobin values in the All 400 mg Analysis Set that show a decrease of approximately 8 g/L at Week 4 that recovered to baseline levels by Week 8, and then subsequently increased to levels that were approximately 10 – 15 g/L above the baseline mean from Week 16 throughout the study. While anaemia was seen during treatment with venetoclax, it was considered not study drug-related rather due to background disease and/or multiple prior therapies, as the incidences decrease over time.

Thrombocytopenia or Platelet Count Decreased

The first onset of thrombocytopenia (or platelet count decreased) was greatest (17.9% of subjects, which represents 43 of the 52 subjects with events) during the first 90 days of venetoclax treatment, and decreased to 1.8% during the next 90 days and to no more than 2.7% for each 90-day interval thereafter. Similarly, the prevalence of thrombocytopenia (or related preferred terms) was greatest during the first 90 days of treatment and decreased during each 90-day interval thereafter.

Figure 18: Mean (± SD) Platelet Count Over Time: Monotherapy R/R CLL (All 400 mg Analysis Set)



CLL = chronic lymphocytic leukaemia; R/R = relapsed or refractory; SD = standard deviation

As for anaemia, while thrombocytopenia was seen during treatment with venetoclax, this was not study drug-related rather due to background disease and/or multiple prior therapies and the incidences of these AEs decrease over time.

Lymphopenia or Lymphocyte Count Decreased

A decrease in lymphocyte count is the desired on-target effect of venetoclax. Lymphopenia occurs due to the on-target effect of venetoclax. Lymphopenia (or lymphocyte count decreased) occurred in 4.6% (11/240) of subjects in the All 400 mg Analysis Set, and the events were grade 3 (n = 4) or grade 4 (n = 3) for the majority of subjects (7/11). No event was serious, and no event led to venetoclax discontinuation, dose interruption, or dose reduction. Additionally, no trend for opportunistic infection was observed. Lymphocyte depletion was seen in non-clinical studies with venetoclax. Changes in subpopulations were addressed and there was an apparent early decrease in T-cells reaching a new set point not later than at 12 weeks and on.

Clinical Chemistry

In the All 400 mg Analysis Set (N = 240), the clinical chemistry results for subjects with grade 0 – 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%). Of the 7 subjects with high glucose at the final assessment, 5 subjects had a history of diabetes. The occurrence of hyperphosphatemia and hypophosphatemia was explained as more likely to be related to TLS or the measures to prevent TLS rather than a pharmacological effect of venetoclax treatment.

Safety in special populations

Table 33: Subject Numbers by Age Across Venetoclax Studies

Study[a]	Subject No.	Age 65 – 74 % (n)	Age 75 – 84 % (n)	Age ≥ 85 % (n)
Total Monotherapy Studies	345	41% (141)	15% (53)	1% (3)
M13-982	158	41% (64)	17% (27)	0.6 % (1)
M12-175	116	41% (47)	14% (16)	1% (1)
M14-032	71	42% (30)	14% (10)	1% (1)
Total Combination Studies	143	41% (59)	8% (12)	1% (1)
M13-365	49	41% (20)	14% (7)	2% (1)
GP28331	49	43% (21)	8% (4)	0
GO28440	45	40% (18)	2% (1)	0
Pharmacokinetic Studies	70	3% (2)	7% (5)	0
Overall Total	**558**	**36% (202)**	**13% (70)**	**< 1% (4)**

Elderly

According to the MAA, the overall incidence of TEAEs, grade ≥ 3 TEAEs, and SAEs was similar across age groups. Among subjects in the All 400 mg analysis set, TEAEs that were reported in at least 10% of subjects < 65 years of age and ≥ 2-fold the rate in subjects ≥ 65 years or vice versa were constipation (7.8% < 65 years, 18.1% > 65 years), hyperphosphatemia (20.6% < 65 years, 10.1% ≥ 65 years), hypophosphatemia (10.8% < 65 years, 3.6% ≥ 65 years), and pruritus (10.8% < 65 years, 5.1% ≥ 65 years). Treatment-emergent AEs that were reported in at least 10% of subjects < 75 years of age and ≥ 2-fold the rate in subjects ≥ 75 years of age or vice versa were vertigo (3.5% < 75 years, 10.0% ≥ 75 years), fall (3.0% < 75 years, 10.0% ≥ 75 years), fluid overload (2.0% < 75 years, 10.0% ≥ 75 years), squamous cell carcinoma of skin (3.5% < 75 years, 17.5% ≥ 75 years), and insomnia (2.0% < 75 years, 10.0% ≥ 75 years).

Table 34: Select Treatment-Emergent Adverse Events by Age Group – Venetoclax All 400 mg Analysis Set

MedDRA Term/Event	Age < 65 Years N = 128 n (%)	Age 65 – 74 Years N = 119 n (%)	Age 75 – 84 Years N = 47 n (%)	Age ≥ 85 Years N = 2 n (%)
Any adverse event	127 (99.2)	118 (99.2)	46 (97.9)	2 (100.0)
Any serious adverse event	63 (49.2)	60 (50.4)	19 (40.4)	2 (100.0)
Fatal	9 (7.0)	11 (9.2)	4 (8.5)	1 (50.0)
Hospitalization	61 (47.7)	57 (47.9)	18 (38.3)	2 (100.0)
Life-threatening	9 (7.0)	11 (9.2)	6 (12.8)	1 (50.0)
Disability	3 (2.3)	3 (2.5)	0	1 (50.0)
Other	4 (3.1)	4 (3.4)	2 (4.3)	0
Leading to venetoclax discontinuation	16 (12.5)	21 (17.6)	7 (14.9)	1 (50.0)
SMQ				
Accidents and injuries (SMQ)	15 (11.7)	17 (14.3)	6 (12.8)	1 (50.0)
Anticholinergic syndrome (SMQ)	0	0	0	0
Cerebrovascular disorders (SMQ)	2 (1.6)	4 (3.4)	1 (2.1)	0
System Organ Class				
Psychiatric disorders (SOC)	12 (9.4)	12 (10.1)	8 (17.0)	0
Nervous system disorders (SOC)	50 (39.1)	47 (39.5)	19 (40.4)	1 (50.0)
Cardiac disorders (SOC)	7 (5.5)	12 (10.1)	8 (17.0)	0
Vascular disorders (SOC)	20 (15.6)	11 (9.2)	8 (17.0)	0
Infections and infestations (SOC)	91 (71.1)	76 (63.9)	34 (72.3)	2 (100.0)
Preferred Term				
Quality of life decreased (PT)	0	0	0	0
Postural hypotension, fall, black outs, syncope, dizziness, ataxia, fractures, etc.[a] (sum of PTs)	16 (12.5)	19 (16.0)	11 (23.4)	1 (50.0)
Constipation	10 (7.8)	26 (21.8)	7 (14.9)	0
Fall	3 (2.3)	4 (3.4)	3 (6.4)	1 (50.0)
Fluid overload	3 (2.3)	2 (1.7)	5 (10.6)	0

Table 35: Select Treatment-Emergent Adverse Events by Age Group – Venetoclax All 400 mg Analysis Set (Continued)

MedDRA Term/Event	Age < 65 Years N = 128 n (%)	Age 65 – 74 Years N = 119 n (%)	Age 75 – 84 Years N = 47 n (%)	Age ≥ 85 Years N = 2 n (%)
Hyperphosphatemia	25 (19.5)	12 (10.1)	6 (12.8)	0
Hypophosphatemia	15 (11.7)	4 (3.4)	0	0
Insomnia	4 (3.1)	4 (3.4)	4 (8.5)	0
Pruritus	11 (8.6)	5 (4.2)	5 (10.6)	0
Squamous cell carcinoma of skin	1 (0.8)	7 (5.9)	9 (19.1)	0
Vertigo	5 (3.9)	4 (3.4)	4 (8.5)	0

PT = preferred term; SMQ = standardised MedDRA query; SOC = system organ class
Fractures CMQ and preferred terms of hypotension, orthostatic hypotension, diastolic hypotension, dizziness, dizziness exertional, dizziness postural, syncope, ataxia, fall.

Renal function: In the All 400 mg Analysis Set, the incidence of these events was lower in subjects with normal renal function, with a rate of 77.8% for any AE compared with ≥ 98% for subjects with mild or moderate impairment; 57.8% for grade ≥ 3 AEs compared with > 71% for mild or moderate impairment; and 28.9% for SAEs compared with 40.2% for mild impairment and 52.9% for moderate impairment. TEAEs that were more frequent in subjects with mild/moderate renal impairment included thrombocytopenia (8.9% normal, 21.6% mild, 17.6% moderate), vomiting (6.7% normal, 11.8% mild, 20.0% moderate), oedema peripheral (6.7% normal, 13.7% mild, 7.1% moderate), neutrophil count decreased (0% normal, 13.7% mild, 3.5% moderate), back pain (4.4% normal, 13.7% mild, 9.4% moderate), urinary tract infection (2.2% normal, 4.9% mild, 10.6% moderate), squamous cell carcinoma of skin (2.2% normal, 3.9% mild, 10.6% moderate). Further, the statistical tables included in the original MAA were updated to include all subjects with normal renal function in the numerators in the analyses of subjects with normal renal function in the 400 mg dose groups, changing the adverse event rates.

Table 36: Overview of TEAEs by Renal Impairment: Venetoclax Monotherapy in R/R CLL

	Venetoclax 400 mg QD					
	All[a]			17p Del[b]		
Type of TEAE	Normal Renal Function[c] N = 45	Mild Renal Impair[c] N = 102	Mod Renal Impair[c] N = 85	Normal Renal Function[c] N = 23	Mild Renal Impair[c] N = 66	Mod Renal Impair[c] N = 69
Any TEAE	44 (97.8)	100 (98.0)	84 (98.8)	22 (95.7)	64 (97.0)	68 (98.6)
CTCAE Grade ≥ 3	33 (73.3)	73 (71.6)	65 (76.5)	16 (69.6)	46 (69.7)	51 (73.9)
Serious TEAEs	18 (40.0)	41 (40.2)	45 (52.9)	10 (43.5)	29 (43.9)	38 (55.1)

After correction of the numerator there is no longer a "signal" related to renal impairment. The SPC and the RMP have been updated as regards renal and hepatic impairment.

Hepatic impairment: No subject had severe hepatic impairment. The overall incidence of TEAEs, grade ≥ 3 TEAEs, and SAEs was similar between subjects with normal hepatic function and subjects with mild/moderate hepatic impairment. Conclusions are limited as only 5 subjects in the All 400 mg Analysis Set had moderate hepatic impairment.

Discontinuations, interruptions and dose reductions of venetoclax due to AES (updated cutoff)

Table 37: TEAEs Leading to Venetoclax Discontinuation in ≥ 2 Subjects (All 400 mg Analysis Set)

	400 mg QD N = 296		
System Organ Class Preferred Term (MedDRA v17.1)	All Subjects[a] n = 296 n (%)	17p Del[b] n = 188 n (%)	BCRi Failure[c] n = 94 n (%)
Any TEAE leading to venetoclax discontinuation[d]	27 (9.1)	20 (10.6)	7 (7.4)
Blood and lymphatic system disorders			
Autoimmune haemolytic anaemia	2 (0.7)	2 (1.1)	0
Thrombocytopenia	2 (0.7)	2 (1.1)	0
General disorders and administration site conditions			
Multi-organ failure	2 (0.7)	2 (1.1)	2 (2.1)

BCRi = B-cell receptor inhibitor; QD = daily; TEAE = treatment-emergent adverse event; 17p del = 17p deletion

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 Arm A, and M14-032.

Events of malignant neoplasm progression were related to progression of the primary disease of CLL and are excluded.

Adverse event preferred terms that led to discontinuation in ≥ 2 subjects in the All 400 mg Analysis Set were autoimmune hemolytic anaemia (n = 2) and thrombocytopenia (n = 2).

The cumulative risk for discontinuation not related to PD is about 12% after about 600 days, relatedness not taken into account. This is compatible with a well-tolerated compound in the treatment of R/R CLL. In none of the cases, discontinuation was preceded by dose reduction and dose reduction was preceded by interruption in 17 of 35 cases.

Adverse Events Leading to Venetoclax Interruption

Interruptions in venetoclax dosing due to TEAEs occurred in 32.9% of subjects in the All 400 mg Analysis Set, and AEs that led to an interruption in ≥ 2% of subjects were neutropenia (3.8%), febrile neutropenia (2.5%), hyperphosphatemia (2.9%), TLS (2.5%), thrombocytopenia (2.1%), nausea (2.1%), vomiting (2.1%), pyrexia (2.1%), and blood creatinine increased (2.1%).

Dose interruptions were rather frequent at ~30%.

Adverse Events Leading to Venetoclax Dose Reduction

Any TEAE leading to venetoclax dose reduction was seen in ~10%. The AEs that led to a venetoclax dose reduction in ≥ 2 subjects were neutropenia (n = 7), febrile neutropenia (n = 3), thrombocytopenia (n = 3), diarrhea (n = 2), vomiting (n = 2), and pneumonia (n = 2).

The dosing status for the 23 subjects who had their venetoclax dose reduced due to AEs in the All 400 mg Analysis Set is summarized as follows:

- 8 subjects subsequently had their dose increased to 400 mg.
- 7 subjects continued dosing at a reduced dose as of the data cutoff date (at 50 – 400 mg).
- 7 subjects continued at a reduced dose until they discontinued venetoclax.
- 1 subject had no dose reduction as of the data cutoff date, but an AE with an onset prior to the data cutoff date led to a dose reduction, and is therefore counted in ISS: Subject 12452 in Study M13-982 dose reduced to 300 mg after the data cutoff date.

Dose interruptions due to AEs occurred in approximately 1/3rd of the study population. In the pivotal study, 11/107 (10.2%) 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 (see clinical efficacy part). This suggests that dose interruptions, even prolonged to >28 days, do not seem to have a major impact on outcome.

Adverse drug reactions

Standard approaches have been applied for adverse drug reactions (ADR) identification

The frequencies of ADRs reported with Venclyxto are summarised in Table 38.

Table 38: Adverse drug reactions reported in patients with R/R CLL treated with Venclyxto

	Number (%) of Subjects				
	Venetoclax 400 mg QD		Venetoclax Any Dose		
System Organ Class Preferred Term (MedDRA v17.1)	All[a] N = 296	17p Del[b] N = 188	All[a] N = 345	17p Del[b] N = 205	BCRi Failure[c] N = 94
Infections and infestations					
Pneumonia	26 (8.8)	16 (8.5)	29 (8.4)	17 (8.3)	10 (10.6)
Upper respiratory tract infection	63 (23.0)	35 (18.6)	94 (27.2)	42 (20.5)	10 (10.6)
Urinary tract infection	24 (8.1)	20 (10.6)	30 (8.7)	21 (10.2)	6 (6.4)
Blood and lymphatic system disorders					
Neutropenia[e]	144 (48.6)	84 (44.7)	168 (48.7)	94 (45.9)	50 (53.2)
Febrile neutropenia	17 (5.7)	9 (4.8)	22 (6.4)	11 (5.4)	10 (10.6)
Lymphopenia[e]	25 (8.4)	11 (5.9)	25 (7.2)	11 (5.4)	13 (13.8)
Anaemia[e]	89 (30.1)	53 (28.2)	97 (28.1)	54 (26.3)	35 (37.2)
Gastrointestinal disorder					
Diarrhoea	115 (38.9)	71 (37.8)	141 (40.9)	80 (39.0)	33 (35.1)
Vomiting	44 (14.9)	25 (13.3)	52 (15.1)	29 (14.1)	13 (13.8)
Nausea	106 (35.8)	60 (31.9)	133 (38.6)	70 (34.1)	30 (31.9)
Constipation	43 (14.5)	22 (11.7)	53 (15.4)	25 (12.2)	11 (11.7)
Metabolism and nutrition disorders					
Tumour lysis syndrome	10 (3.4)	8 (4.3)	18 (5.2)	10 (4.9)	3 (3.2)
Hyperphosphataemia[d]	53 (17.9)	26 (13.8)	55 (15.9)	27 (13.2)	18 (19.1)
Hyperkalaemia[d]	28 (9.5)	18 (9.6)	30 (8.7)	18 (8.8)	14 (14.9)
Hyperuricemia[d]	15 (5.1)	8 (4.3)	19 (5.5)	9 (4.4)	9 (9.6)
Hypocalcaemia[d]	26 (8.8)	11 (5.9)	27 (7.8)	11 (5.4)	11 (11.7)
General disorders and administration site conditions					
Fatigue	77 (26.0)	44 (23.4)	101 (29.3)	54 (26.3)	26 (27.7)
Investigations					
Blood creatinine increased	22 (7.4)	13 (6.9)	22 (6.4)	13 (6.3)	8 (8.5)

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

e. Subjects with R/R CLL in Studies M13-982, M12-175 Arm A, and M14-032.

f. Subjects with R/R CLL harboring 17p del; Studies M13-982, M12-175 Arm A, and M14-032.

g. Subjects with R/R CLL who previously failed BCRi therapy; Studies M13-982, M12-175, and M14-032.

h. Data for preferred terms were combined as follows:
Hyperuricemia: preferred terms of hyperuricaemia and blood uric acid increased
Hyperkalemia: preferred terms of hyperkalaemia and blood potassium increased
Hyperphosphatemia: preferred terms of hyperphosphataemia and blood phosphorus increased
Hypocalcemia: preferred terms of hypocalcaemia and blood calcium decreased.

i. Data for preferred terms were combined as follows:
Neutropenia: preferred terms of neutropenia and neutrophil count decreased
Lymphopenia: preferred terms of lymphopenia and lymphocyte count decreased
Anaemia: preferred terms of anaemia and haemoglobin decreased.

2.6.1. Discussion on clinical safety

The overall clinical safety evaluation of venetoclax included a total of 553 subjects who received at least 1 dose of venetoclax. This safety population includes 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 safety results from the 3 monotherapy CLL studies (pivotal Study M13-982 and supportive studies M12-175 and M14-032) were largely similar. The safety evaluation of 400 mg QD venetoclax monotherapy is based on the pooled dataset of all subjects who received 400 mg venetoclax in the 3 monotherapy studies listed above (N = 289 subjects for all doses; N = 240 for the 400 mg dose). The monotherapy substudy in subjects with NHL (Arm B of Study M12-175; N = 106) provides comparative data to help differentiate CLL-related AEs and risk factors from those attributable to venetoclax.

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.

In the All 400 mg Analysis Set (n=240), 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%), hyperphosphatemia (14.6%), constipation (13.8%), cough (13.3%), hypokalaemia (12.1%), oedema peripheral (10.8%), and back pain (10.0%).

Adverse events with a reasonable possibility of being related to venetoclax that occurred in ≥ 10% of subjects in the All 400 mg Analysis Set were neutropenia (31.3%), nausea (23.3%), diarrhoea (18.8%), fatigue (12.9%), hyperphosphatemia (11.3%), thrombocytopenia (10.4%), and anaemia (10.4%).

Adverse events grade 3/4 and reported in ≥ 5% of subjects in the All 400 mg Analysis Set were neutropenia (36.3%), anaemia (17.5%), thrombocytopenia (13.3%), neutrophil count decreased

(6.7%), febrile neutropenia (5.4%), and pneumonia (5.0%). Grade 3/4 infectious events (SOC) occurred in 17.5 % and Neoplasms (benign, malignant or unspecified) in 9.2%.

Serious TEAEs were reported in 44.2% of subjects in the All 400 mg Analysis Set, and SAEs reported in at least 2% of subjects were malignant neoplasm progression (5.0%), pneumonia (5.0%), febrile neutropenia (4.6%), pyrexia (3.3%), autoimmune haemolytic anaemia (2.9%), anaemia (2.1%), and TLS (2.1%). Serious infectious events (SOC) occurred in 17.9% and SOC Neoplasms (benign, malignant and unspecified) in 9.6%.

Safety findings were broadly those expected in this study population and were generally consistent across subpopulations including All doses (n=289), All del17p (n=177), and BCRi-failures (n=46).

In general, TEAEs had the highest incidence at initiation of therapy (Day 1-90) and abated thereafter.

A total of 7 deaths, out of the 18 fatal TEAEs in the All 400 mg Analysis Set (N = 240), had causes other than disease progression, as assessed by the investigator. The causes of death were variable and consistent with the patient population with multiple risk factors including advanced CLL, and were all considered by the investigator to be not related or probably not related to study drug. Three additional deaths were reported in other dose groups (venetoclax monotherapy), and 1 of these deaths was considered possibly related to study drug. This event was a sudden death that occurred in the setting of TLS at the highest dose (1200 mg) in the clinical development program prior to the implementation of the current dosing regimen and prophylactic measures.

An additional 18 deaths from non-TEAEs (e.g., AE that was fatal had an onset > 30 days post venetoclax dosing) were reported in the monotherapy analysis sets in R/R CLL. These deaths included 14 due to disease progression and 4 subjects (all in Study M12-175) with additional causes and occurred between Post-Treatment Day 43 and 486. In the venetoclax combination therapy studies in R/R CLL (Studies M13-365, GO28440, and GP28331), a total of 2 fatal TEAEs were reported, both in Study M13-365. One of these was due to hyperkalaemia in the setting of TLS.

A total of 8 fatal TEAEs were reported in subjects with NHL who received venetoclax monotherapy in Study M12-175 (Arm B) and were deemed secondary to malignant neoplasm progression for 7 subjects. No deaths were reported in the Phase 1 clinical pharmacology studies.

Discontinuation of venetoclax due to TEAEs not related to disease progression occurred in 21/240 (8.8%) of subjects in the All 400 mg Analysis Set and included 6 deaths. Dose interruptions due to TEAE were rather frequent at ~30% and dose reductions were performed in ~10%. About a third of the subjects who had a dose reduction due to AEs could subsequently increase the dose to 400 mg. In the main cohort of the pivotal study, 104/107 subjects achieved the target dose of 400 mg.

Non-clinical studies had identified a maximum recommended starting dose of 200 mg dose. Following laboratory TLS in all 3 first subjects dosed with venetoclax 100 or 200 mg in the dose finding study M12-175, successive amendments have been implemented to minimize the risk for TLS. These measures include ramp-up dosing over 5 weeks, starting at 20 mg with final dose of 400 mg in CLL/SLL subjects, enhanced monitoring, TLS prophylaxis measures, and additional guidance for investigators and are adequately described in the SmPC (see section 4.8) and RMP.

Of a total of 66 subjects enrolled following the Current Amendment, including 59 subjects who have completed the initial ramp-up period, TEAEs of TLS were reported in 6.1% (4/66) of subjects, with no events of Clinical TLS (significant impairment of kidney function, cardiac arrhythmia/sudden death, and/or seizure; please see above). It appears, then, that the current scheme for ramp-up dosing has been successful in mitigating the risk for TLS upon treatment of R/R CLL with venetoclax. TLS is an important identified risk in the proposed venetoclax RMP. Tumour lysis syndrome, including fatal

events, has occurred in patients with previously treated CLL with high tumour burden when treated with Venclyxto.

The risk of TLS is a continuum based on multiple factors, including comorbidities. Patients with high tumour burden (e.g., any lymph node with a diameter ≥5 cm or high ALC ≥25 x 10^9/L) are at greater risk of TLS when initiating venetoclax. Reduced renal function (CrCl <80 mL/min) further increases the risk. Patients should be assessed for risk and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricaemics. Blood chemistries should be monitored and abnormalities managed promptly. Dosing should be interrupted if needed (see section 4.2). More intensive measures (intravenous hydration, frequent monitoring, hospitalisation) should be employed as overall risk increases. The instructions for "Prevention of tumour lysis syndrome" should be followed (see section 4.2). Concomitant use of Venclyxto with strong or moderate CYP3A inhibitors increases venetoclax exposure and may increase the risk for TLS at initiation and during the dose-titration phase (see sections 4.2 and 4.3). Also inhibitors of P-gp or BCRP may increase venetoclax exposure (see section 4.5).

In the All 400 mg Analysis Set, neutropenia AESIs were reported in 46.7% (112/240) of subjects. While neutropenia AESIs were grade ≥ 3 in 42.1% (101/240) of subjects, serious events occurred at a lower incidence of 5.8% (14/240). In the monotherapy studies, mean ANC-values appear more or less stationary following an initial decrease at week 4. This is despite the use of G-CSF in a significant proportion of subjects. Neutropenia AESIs led to venetoclax dose interruption in 5.8% (14/240) of subjects, and venetoclax dose reduction in 4.2% (10/240) of subjects. No subject discontinued venetoclax because of neutropenia AESIs. Neutropenia is an important identified risk with venetoclax administration (see RMP) and has been labelled as a common AE in section 4.8 of the SmPC.

In the All 400 mg Analysis Set, infections were reported in 65.4% (157/240) of subjects and the events were grade 1 or 2 for the majority of these subjects (114/157; 72%). The most common (≥ 5%) infection preferred terms were upper respiratory tract infection (21.7%), nasopharyngitis (9.2%), pneumonia (7.5%), and urinary tract infection (6.3%). The most common preferred terms among grade 3/4 infections were pneumonia (5.0%), upper respiratory tract infection (1.3%), and cellulitis (1.3%). The infection AESIs were serious in 17.9% (43/240) of subjects, and led to venetoclax discontinuation in 0.8% (2/240) of subjects, interruption in 8.8% (21/240) of subjects, and dose reduction in 2.1% (5/240). Overall, the pattern of infectious AE recorded in the monotherapy studies seem to be expected in a study population of advanced CLL. Serious infection is included as an important potential risk in the RMP.

In the All 400 mg Analysis Set, second primary malignancy events were reported in 11.7% (28/240) of subjects. Of these 28 subjects, 18 had non-melanoma skin cancers, and 10 had other second primary malignancies with no pattern to the specific malignancy type. In the RMP, carcinogenicity is included as missing information. A causal association of venetoclax to second primary malignancy cannot be established with the limited number of subjects exposed to venetoclax, and the relatively short follow-up time.

Autoimmunity is of common occurrence in the CLL population. In the All Doses Analysis Set, autoimmune haemolytic anaemia (AIHA) occurred in 4.5% (13/289) of subjects and immune thrombocytopenic purpura (ITP) occurred in 3.5% (10/289) of subjects, whereas the incidence in NHL subjects (Arm B of Study M12-175) was 0.9% (1/106) for AIHA and 0% (0/106) for ITP.

The events of AIHA led to venetoclax dose interruption in 3 subjects, venetoclax dose reduction in 1 subject, and venetoclax discontinuation in 2 subjects. The events of ITP led to venetoclax dose

interruption in 4 subjects and venetoclax dose reduction in 1 subject. No events led to venetoclax discontinuation.

According to the literature, disease progression due to Richter's syndrome, a clinical-pathologic transformation of CLL to an aggressive lymphoma, occurs over time in approximately 15% (5% – 20%) of cases of CLL with the risk being higher among subjects with R/R CLL. Per protocol, all subjects who showed clinical signs of progression due to Richter's syndrome were to be discontinued. Of the 289 subjects in the R/R CLL All Doses Analysis Set, 29 subjects were discontinued because of progression of disease that included Richter's syndrome: 15 in Study M12-175, 13 in Study M13-982, and 1 in Study M14-032. The possibility of ongoing transformation to Richter's syndrome prior to initiating venetoclax cannot be ruled out in 13 of the 29 subjects where Richter's syndrome was reported within 6 months of initiating venetoclax therapy. The possibility of ongoing transformation to Richter's syndrome prior to initiating venetoclax cannot be ruled out in 13 of the 29 subjects where Richter's syndrome was reported within 6 months of initiating venetoclax therapy. Updated data on Richter's transformation further reveal that among the 345 subjects with CLL treated with any dose of venetoclax monotherapy and included in the updated safety analyses, 37 cases were identified to have RT in course of CLL disease progression. The current incidence of RT in studies with venetoclax monotherapy is 10.7%; the incidence of RT among non-responders (20.7%) was higher than among subjects with documented clinical response by investigator (6.9%). The mean onset of RT from venetoclax initiation was 290.5 (range: 9 – 700) days, with 14 subjects diagnosed with RT within 6 months after first dose of venetoclax. The majority of the subjects had multiple risk factors (e.g., R/R disease, 17p del, multiple prior cytotoxic therapies, prior fludarabine-based therapy). Considering the limited number of patient years in the venetoclax development program, the incidence of Richter's syndrome appears high.

Risk factors (number of prior lines, del17/TP53, fludarabine resistance etc.) associated with the risk of RT were enriched in the venetoclax studies and proactive diagnostics was made part of the study design. This makes historical comparisons hard to evaluate, but the transformation rate was clearly on the high side. In the majority of cases, RT is part of clonal evolution, but may also occur as a de novo DLBC lymphoma histologically indistinguishable from clonally evolved DLBCL, but with genetic characteristics dissimilar to the CLL clone, and uncommon transformations to Hodgkin. Whether risk factors for clonally related and unrelated are the same appears less well understood. Ongoing and projected studies in less advanced stages may shed further light onto this issue (see RMP). Although comparison of the incidence of Richter's syndrome among patients in the venetoclax program to available data in the literature are challenging, Richter's transformation is considered as an important potential risk of treatment with venetoclax.

Diarrhoea occurred in 35% of subjects in the All 400 mg subpopulation, nausea occurred in 33% of subjects and vomiting occurred in 14.6%. The majority of gastrointestinal AEs were grade ≤2 and manageable with no treatment or with standard medical care. Only 1 subject discontinued venetoclax because of diarrhoea (due to grade 2 diarrhoea and vomiting). A review of AEs over time indicates that the first onset occurred within the first 90 days of treatment for the majority of subjects who experienced gastrointestinal AEs. Tolerance may be different in individuals with pre-existing gastrointestinal conditions eg IBD.

Consistent with the age of the study population (median of 66 years), 60.8% of subjects in the All 400 mg Analysis Set had medical histories of diseases or conditions reported in the cardiovascular system prior to starting venetoclax. A total of 8 subjects in the All 400 mg Analysis Set experienced SAEs in the cardiac disorders SOC including 4 cases with atrial fibrillation or atrial flutter. Overall, the number and scope of cardiac events appear to be within the expected range for the study population.

Adverse events in the haemorrhages SMQ (narrow search) were reported in 13.8% (33/240) of subjects in the All 400 mg Analysis Set and the events were grade 3 (n = 5) or 4 (n = 4) for 9 subjects (4%). These events were serious in 6 subjects, all considered to have no reasonable possible relationship to venetoclax by the investigator. Of the 9 subjects with grade ≥ 3 events, 6 subjects had ITP. The incidence of AEs in the haemorrhage SMQ in the All 400 mg Analysis Set in subjects on concurrent anticoagulant and/or antiplatelet medications 16.8% compared with 11.5% in subjects not on concurrent anticoagulants. The reported cases of haemorrhage do not seem to indicate an increased bleeding risk associated with venetoclax therapy in CLL.

There were few events of severe or serious adverse events with hepatobiliary disorders. One fatal case was in an 85 y old subject with preexisting elevations of LFT and prostate cancer, and 3 cases with elevations of ALT or AST >10 x ULN had concomitant multiorgan failure or TLS. A medical review did not identify any subject meeting Hy's law in the All 400 mg Analysis Set.

Lymphopenia (or lymphocyte count decreased) occurred in 4.6% (11/240) of subjects in the All 400 mg Analysis Set, and the events were grade ≥3 for the majority of subjects (7/11).

In non-clinical studies, the key findings observed following venetoclax administration were decreased lymphocyte count, decreased red blood cell mass (at higher doses), testicular germ cell depletion in dogs, and embryo-fetal toxicity in mice, which were consistent with venetoclax's Bcl-2 inhibition. Discolouration (white) of fur was seen in some animals.

Although only a few events of white hair discolouration have been reported in clinical trial subjects, the data are confounded by large as the majority of subjects in clinical trials being elderly.

A general safety update (10 February 2016 data cut) has been provided for all subjects receiving 400 mg venetoclax (All 400 mg Analysis Set, N = 296). The median follow-up for venetoclax increased by 1 month to 11.4 months (previously 10.3 months), with approximately 100 subjects who have received venetoclax for over 1 year. Longer exposure (up to 2 years) is available for at least 28 subjects. Excluding disease progression, about 10% of patients discontinued venetoclax after median about 1 year of therapy indicating good tolerability in pre-treated CLL patients. A safety update with a 10 February 2016 data cut off has been provided for all subjects receiving 400 mg venetoclax (All 400 mg Analysis Set, N = 296). The median follow-up for venetoclax increased by 1 month to 11.4 months (previously 10.3 months), with approximately 100 subjects who have received venetoclax for over 1 year. Longer exposure (up to 2 years) is available for at least 28 subjects. Excluding disease progression, about 10% of patients discontinued venetoclax after median about 1 year of therapy indicating good tolerability in pre-treated CLL patients.

Confirmation of overall safety with a specific focus on Richter's transformation will be derived from Study GO28667 (MURANO), this is a multicenter, phase III, open-label, randomised study in elapsed/refractory CLL patients to evaluate the benefit of venetoclax in combination with rituximab compared with bendamustine plus rituximab.

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

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

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The main safety finding in the venetoclax monotherapy studies in CLL was the risk of TLS, especially at the initiation of treatment and most pronounced in subjects with a high tumour burden. A slow ramp-up dosing during the first 5 weeks combined with close patient monitoring seems largely to have overcome this risk, but there may still be a concern in select patients. Other safety events were those encountered in advanced CLL eg infections, cytopenias and transformation. Incidences were mostly within the expected range for the study population and no clear causal link between transformation events and venetoclax therapy has been established, also due to the lack of comparative data.

Discontinuations for TEAEs unrelated to disease progression were <10%, which seems acceptable in this group of patients.

In conclusion, albeit further analyses are still requested, the safety profile of venetoclax in subjects with del17p-CLL, and in those with R/R CLL, seems to be clinically manageable.

Generally, the evaluation of the safety profile of venetoclax is hampered by the fact the underlying disease may be the major contributor to, e.g. infectious events, ITP and squamous carcinoma of the skin. High age is an obvious risk factor for vascular events. Therefore safety data from a comparative, randomised study would be necessary.

The CHMP considers the following measures necessary to address issues related to safety:

- PASS Study GO28667 (MURANO) in relapsed/refractory patients with chronic lymphocytic leukaemia to evaluate the safety of venetoclax plus rituximab compared with bendamustine plus rituximab.

Additional safety data needed in the context of a conditional MA
The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

- The applicant should provide further data on safety for study M14-032 of venetoclax in chronic lymphocytic leukaemia patients relapsed after or refractory to treatment with B-cell receptor signaling pathway inhibitor therapy.

2.7. Risk Management Plan

Safety concerns
Table 39: Summary of the safety concerns

Summary of Safety Concerns for the Target Population	
Important identified risks	• Tumour lysis syndrome • Neutropenia
Important potential risks	• Embryofoetal toxicity • Testicular toxicity • Medication error • Serious infection • Richter's transformation • DDI (CYP3A inducers, CYP3A inhibitors)
Missing information	• Carcinogenicity studies

	• Safety in severe hepatic impairment • Safety in severe renal impairment • Safety in long-term exposure (> 12 months)

Pharmacovigilance plan

Table 40: Summary of the pharmacovigilance plan

Study/Activity Type, Title and Category (1 – 3)	**Objectives**	**Safety Concerns Addressed**	**Status (Planned, Started)**	**Date for Submission of Interim or Final Reports (Planned or Actual)**
Study GO28667 (MURANO) Multicenter, Phase III, Open-Label, Randomised Study in Relapsed/Refractory Patients with Chronic Lymphocytic Leukaemia to Evaluate the Benefit of GDC-0199 (ABT-199) Plus Rituximab Compared with Bendamustine Plus Rituximab Category 1	Evaluate the efficacy of venetoclax and rituximab compared with BR in subjects with R/R CLL	Overall safety profile (provide comparator data) Richter's transformation	Ongoing	March 2018

Study/Activity Type, Title and Category (1 – 3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
M14-032 A Phase 2 Open-label Study of the Efficacy and Safety of ABT-199 (GDC-0199) in Chronic Lymphocytic Leukaemia Subjects with Relapse or Refractory to B-cell Receptor Signaling Pathway Inhibitor Therapy Category 2	Objective: Assess the efficacy and safety of venetoclax monotherapy in subjects with CLL relapsed after or refractory to treatment with ibrutinib or idelalisib	Safety in long-term exposure (> 12 months) of venetoclax Second primary malignancy and Richter's transformation in longer exposure to venetoclax monotherapy	Ongoing	March 2018
M13-982 A Phase 2 Open-Label Study of the Efficacy of ABT-199 in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukaemia Harboring the 17p Deletion Category 3	Objective: Evaluate the efficacy of venetoclax monotherapy in subjects with R/R CLL in the presence of 17p del or *TP53* mutations	Safety in long-term exposure (> 12 months) of venetoclax Second primary malignancy and Richter's transformation in longer exposure to venetoclax monotherapy	Ongoing	June 2018

Study/Activity Type, Title and Category (1 – 3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
M12-175 A Phase 1 Study Evaluating the Safety and Pharmacokinetics of ABT-199 in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukaemia and Non-Hodgkin Lymphoma Category 3	Objective: Assess the safety profile; characterise PK; determine MTD, RPTD, and lead-in period regimen of venetoclax monotherapy in subjects with R/R CLL or NHL	Safety in long-term exposure (> 12 months) of venetoclax Second primary malignancy and Richter's transformation in longer exposure to venetoclax monotherapy	Ongoing	September 2019
M15-342 A Study to Evaluate the Safety and Pharmacokinetics of a Single Dose of Venetoclax in Female Subjects with Mild, Moderate, or Severe Hepatic Impairment Category 3	To assess the safety and pharmacokinetics of venetoclax following oral administration of a single dose of venetoclax in subjects with various degrees of hepatic impairment	Use in patients with severe hepatic impairment	Ongoing	March 2018

Study/Activity Type, Title and Category (1 – 3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Prospective Observational Cohort Study to Assess the Safety of Venetoclax in the Swedish Cohort of Chronic Lymphocytic Leukaemia Patients Category 3	To assess the long-term safety of venetoclax using a prospective cohort containing both venetoclax exposed and non-exposed patients.	Safety in long-term exposure (> 12 months) of venetoclax	Planned	Interim analyses planned every second year over a study period of 8 years Final report planned December 2025
Clinical drug-drug interaction study with an oral contraceptive Category 3	Open-label study to assess the effect of venetoclax on the pharmacokinetics of oral contraceptive in haematologic malignancy patients	Use in patients who require oral contraceptives	Planned	Date for submission cannot be specified since the Agency accepted to conduct the oral contraceptive drug-drug interaction study when the indication is potentially widened to a younger population
In vitro study to evaluate the potential of venetoclax to induce CYP1A2 and CYP2B6 Category 3	To evaluate the potential of venetoclax to induce CYP1A2 and CYP2B6	To better characterize the risk for induction of these enzymes.	Planned	March 2017

Risk minimisation measures

Routine risk minimisation measures are proposed.

Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
Tumour lysis syndrome (TLS)	Posology and method of administration, including prophylactic measures for TLS, are described in section 4.2 of the SmPC. Warnings and precautions for TLS are listed in section 4.4 of the SmPC. Interaction with other medicinal products is described in section 4.5 of the SmPC. TLS is described in section 4.8 of the SmPC. Other routine risk minimisation measures: Prescription only medicine Use of treatment should be initiated and supervised by specialists Packaging design and language to facilitate adherence to the dose titration schedule Package leaflet	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Neutropenia	Posology and method of administration are described in section 4.2 of the SmPC. Warnings and precautions for neutropenia are listed in section 4.4 of the SmPC. Neutropenia is listed as a very common adverse reaction in section 4.8 of the SmPC. Other routine risk minimisation measures: • Prescription only medicine. • Use of treatment should be initiated and supervised by specialist • Package leaflet	None
Embryofoetal toxicity	Language concerning embryofoetal toxicity is included in section 4.6 and section 5.3 of the SmPC. Other routine risk minimisation measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Package leaflet	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Medication error	Posology and method of administration are described in section 4.2 of the SmPC. Language concerning overdose is included in section 4.9 of the SmPC. Other routine risk minimisation measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Each carton will be dispensed weekly to the patient during the first 4 weeks of the dose titration • Labeling and packaging layout (immediate and outer packaging) has been designed to minimise medication errors • Package leaflet	None
Serious infection	Posology and method of administration are described in section 4.2 of the SmPC. Supportive measures for infections associated with neutropenia are described in section 4.4 of the SmPC. Observed infections and infestations are tabulated in section 4.8. Other routine risk minimisation measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialist • Package leaflet	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Richter's transformation	• Posology and method of administration are described in section 4.2 of the SmPC. • Prescription only medicine • Use of treatment should be initiated and supervised by specialist	None
Drug-drug interaction with CYP3A inducers, CYP3A inhibitors	Language concerning DDI contraindications for strong CYP3A inhibitors during the dose-titration phase, as well as preparations containing St. John's wort (CYP3A inducer), is listed in section 4.3 of the SmPC. Additional instructions regarding the concomitant use of CYP3A4 inducers are provided in section 4.4 of the SmPC. DDIs that require dose adjustments or monitoring are listed in section 4.2 and section 4.5 of the SmPC. Other routine risk minimisation measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Package leaflet	None
Carcinogenicity studies	Language concerning carcinogenicity is included in section 5.3 of the SmPC. Other routine risk minimisation measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Safety in severe hepatic impairment	Section 4.2 of the SmPC advises that safety and efficacy have not yet been established in certain populations. Other routine risk minimisation measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Package leaflet	None
Safety in severe renal impairment	Section 4.2 of the SmPC advises that safety and efficacy have not yet been established in certain populations. Other routine risk minimisation measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Package leaflet	None
Safety in long-term exposure (> 12 months)	• Median duration of treatment is included in section 5.1 of the SmPC • Prescription only medicine • Use of treatment should be initiated and supervised by specialists	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 2.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Venclyxto (venetoclax) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Beneficial effects

Updated results from Study M13-982 - an ongoing single-arm study evaluating the efficacy and safety of venetoclax monotherapy 400 mg daily in subjects with R/R CLL with 17p del that includes the *TP53* locus- showed an ORR of 82.4 % in the safety expansion (SE) cohort 74.8 % in the main cohort; 77.2% in both cohorts with CR of 15.7; 19.6% 18.4% respectively. Radiologic response was observed at the first visit for most subjects in the main cohort, whilst CR evolved after prolonged treatment, up to several months.

Durability of response was long, resulting in PFS at 24 months 69% (95% CI 60; 77%) in the main cohort and PFS at 12 months in the SE cohort being 80% (95% CI 66; 89%). In the main cohort, documented minimal residual disease (MRD) negativity in peripheral blood and on therapy was about 26%, i.e. higher than the complete remission rates. No obvious subgroup-related differences were reported.

In open-label, multi-centre study Study M14-032 evaluating 400 mg of venetoclax in subjects with CLL who were refractory or intolerant to treatment with either ibrutinib or idelalisib, updated ORR results (10 June 2016) were at 69.8 % (IRC) and 67.4% (Inv) in ibrutinib failed cohort and 61.9% / 57.1% in the idelalisib failed cohort. CR at 2.3 % (IRC); 7% (Inv) was seen at the ibrutinib-failed group whereas in the idelalisib – failed group the IRC has seen no CR, the investigators have assessed as 14.3% of

patients achieved CR. The updated analyses ORR results of 10 June 2016, appear similar after idelalisib and ibrutinib failure.

Subjects who had relapse while on therapy or had lack of response within 6 months of treatment with a BCRi were determined as having refractory disease. The majority of subjects in both arms were previously refractory to BCRi therapy, although proportionally more subjects who entered Arm B discontinued idelalisib due to intolerance. In refractory disease the ORR was about 67% after ibrutinib failure and about 71% after idelalisib failure. Status with respect to del17p/TP53 apparently did not affect response rates. Altogether 40 patients had failed both chemoimmunotherapy (CIT) and BCRi and in this group the ORR was 25/40 (95% CI 46; 77%).

Updated data from the supportive, dose escalation and safety expansion Phase 1 study M12-175 show an ORR of 82% in the broader relapsed/refractory (R/R) CLL population. Current estimate for PFS at 24 months is 62% (10 June, 2016).

Median durations of exposure in the studies M13-982 and M12-175 are considered sufficiently long for a reasonably precise estimate of benefit.

Uncertainty in the knowledge about the beneficial effects.

As approvals of ibrutinib and idelalisib were relatively recent, the data on patient outcome after failure on a BCRi is rather limited. Although the anti-tumour activity of venetoclax in BCRi refractory patients independent of 17p deletion/TP53 mutation was acknowledged, the non-comparative and limited data due to low number of subjects and limited follow-up time in this population represents an uncertainty.

Moreover, the patient population in this study is more heterogeneous, e.g. in terms of the number of prior therapies, but it is agreed that prior failure on idelalisib, ibrutinib or CIT has no major influence on reported response rates and that del17p/TP53 status seems not to be of importance. The latter has also replicated in M12-175 and ex vivo. Very few patients have been treated >2y and PFS and OS data are still immature.

Therefore, additional efficacy data would be needed as confirmatory and will be provided from the expanded study M14-032 (first cohort PFS at 48 weeks and second cohort ORR and PFS at 36 weeks) are expected in the context of a conditional MA in order to expand the (See Annex II and RMP). Study M14-032 was recently amended to include a second cohort comprising an additional 60 BCRi failure patients to further assess the safety and efficacy of venetoclax in patients with prior BCRi failure and this will also provide additional efficacy and safety data in post-BCRi 17p/TP53 mutation negative CLL patients. Currently 55 patients are enrolled (23 subjects with del 17p/TP53mut; 30 patients without del 17p/TP53mut).

Risks

Unfavourable effects

A general safety update was submitted for all subjects receiving 400 mg venetoclax (All 400 mg Analysis Set, N = 296). In addition, updated safety data for 17p del subjects receiving 400 mg venetoclax (N = 188) and subjects with previous BCRi failures receiving 400 mg venetoclax (N = 94). The main safety concern in the venetoclax monotherapy studies in CLL was the risk of tumour lysis syndrome (TLS), especially at the initiation of treatment and most pronounced in subjects with a high tumour burden. Following protocol amendments that included a slow ramp-up dosing during the first 5 weeks, close monitoring and other measures, the risk for clinical TLS seems largely contained at an reported incidence of about 3%.

Dose reductions were undertaken in a total of about 10% mainly for neutropenia and thrombocytopenia, but also, e.g. for diarrhoea. Dose interruptions were more common; close to one in three subjects reported interruption for adverse events. The cumulative discontinuation rate after about 600 days was about 13%, which is considered low.

As expected in the treatment of CLL, infectious events were very common and altogether there were about 20% of infectious events classified as SAEs, mainly pneumonia.

Adverse events with a reasonable possibility of being related to venetoclax that occurred in ≥ 10% of subjects in the All 400 mg Analysis Set were neutropenia (≈30%), nausea (≈20%), diarrhoea (≈20%), fatigue (≈10%), thrombocytopenia (≈10%), and anaemia (≈10%).

Uncertainty in the knowledge about the unfavourable effects

Assessment of the safety profile of venetoclax is compromised by the lack of controlled data as manifestations of CLL include cytopenias, infectious events, immune deficiencies, second primary malignancies, etc.

Tumour progression is inherent in CLL, including transformation/Richter's syndrome. The incidence [~10%] of Richter's syndrome appears somewhat high compared with historical data, but the studies enrolled patients at high risk and specific measures were undertaken to identify cases of transformation. Even though no potential underlying mechanistic explanation has been identified, Richter's transformation should be considered an important potential risk. Ongoing and projected studies in less advanced CLL may shed further light onto this issue.

The data on long term safety effects put in relation to the durability of response are limited, as is the clinical experience on the development of resistance for venetoclax.

There was an apparent about 50% reduction in numbers of circulating T-cells. This may at least partly be explained by "contamination" of the FACS analyses by apparently CD3/CD19 co-expressing cells, i.e. cells with B and T-cell markers. Re-analyses are ongoing and will be provided as recommended by the CHMP.

Safety data from the MURANO study are expected to confirm the safety profile of venetoclax in comparison with bendamustin, the data should be discussed in the light of studies M12-075, M13-982, and M14-032.

Effects Table for Venclyxto in the treatment of adult patients with chronic lymphocytic leukaemia (CLL) in the presence of 17p deletion or TP53 mutations.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ORR	Response rate (IRC assessed)	%	≈80	NA	Convincing	Study M13-982
CR + CRi	Complete remissions (including CR with incomplete bone marrow	%	≈18	NA	Previously not achieved with monotherapy in high-risk CLL (17p del)	Study M13-982

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
	recovery)					
PFS 2 y.	KM-estimate	%	62%	NA		Study M13-982
OS 2 y	KM-estimate	%	85%	NA		Study M13-982
MRD-neg	Minimal residual disease negativity		28/117 (peripheral blood)	NA	On therapy results.	Study M13-982
ORR	Response rate (IRC assessed)	%	≈70 (30/43) (ibrutinib) ≈50 (10/21) (idelalisib)	NA	Heterogeneous population Intolerance/resistance	Study M14-032
PFS 6 m.	KM-estimate	%	≈80			Study M14-032
Unfavourable Effects						
TEAE (updated cutoff)	All adverse events	%	99	NA	No comparative data (single arm studies)	All 400 mg Analysis Set (n=296)
TEAE grade ¾ (updated cutoff)	Severe TEAE	%	76	NA	No comparative data (single arm studies)	All 400 mg Analysis Set (n=296)
SAE (updated cutoff)	Serious AE	%	49	NA	No comparative data (single arm studies)	All 400 mg Analysis Set (n=296)
Deaths (original cutoff)	Fatal TEAE	N (%)	18 (7.5)	NA	No comparative data (single arm studies)	All 400 mg Analysis Set (n=240)

Abbreviations: IRC, Independent Review Committee

Benefit-Risk Balance

Importance of favourable and unfavourable effects

In early stage CLL, approximately 5% to 10% of patients have a 17p del and/or *TP53* mutation; this rate increases with treatment lines up to 40% in advanced refractory CLL and is associated with low activity/resistance to chemo- and chemo-immuno therapy.

No randomised comparative studies have been submitted in support of this MAA, but durable objective responses lead to improvement in the symptomatology, including haematological parameters and is considered an informative outcome measure in patients with CLL evaluable also in single arm studies.

At the start of the clinical development of CLL for venetoclax, there were no satisfactory therapeutic options for CLL with 17p del/TP53-mutations, apart from allogeneic SCT suitable for very few, younger patients in good general health after achieving a good response to toxic regimen. Available chemo-immuno therapies (ICT), are associated with short lived partial responses and were the only alternative for the great majority of patients. In fact, and probably as a result of the poor response seen retrospectively in 17p del CLL to known treatments, no dedicated prospective studies were undertaken in this subgroup.

In the last few years, novel therapies have emerged showing durable responses in a significant proportion in this high-risk subgroup of CLL leading to the licensure of idelalisib and ibrutinib. Study M14-032 was undertaken in an heterogeneous late-line population of patients failing BCRi:s (n=63), resistance and intolerant, del 17p positive and negative) and ICT (n=40) . As these BCRis (idelalisib and ibrutinib) have only recently entered clinical practice, data on BCRi failed/discontinuing patients are limited.

In patients failing BCRis without the 17pdel/TP53mut there are might be more therapeutic options available, such as CIT. These patients can also be treated with the alternate kinase inhibitor, and based on retrospective data this latter has recently been reported to provide response rates of 6/12 to idelalisib-based therapy after ibrutinib failure and 10/13 to ibrutinib-based therapy after idelalisib failure (Mato, ASH 2015), but patient numbers are low and follow up is brief.

As for the unfavourable effects, TLS was identified early on as an important and serious risk with venetoclax, especially at the initiation of therapy. This risk now seems largely to have been contained through preventive measures including ramp-up dosing and involving risk-staging and close monitoring.

The risk of infections is inherent in advanced CLL and is to be a remaining concern during venetoclax therapy. The pattern of infections reported in the present studies, however, seems to agree with that observed in many previous studies in R/R CLL and the rate of opportunistic infections is inconspicuous.

Discussion on the benefit-risk assessment

On the basis of the totality of the data including those in BCRi experienced patients the applied indication was revised to "Venclyxto is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) in the presence of 17p deletion or TP53 mutations, or who are unsuitable for or have failed a B-cell receptor pathway inhibitor."

As there are differences in the safety profiles comparing venetoclax with idelalisib and ibrutinib, and possible anticipated differences in tolerance, the defined use of venetoclax in this population is clinically meaningful.

The presence of deletion 17p and TP53 mutations do not affect the activity of venetoclax. In addition prior therapy with available BCRIs and CIT appears not to affect the activity of venetoclax to a major degree. It is acknowledged that data are sparse (n=40), but based on submitted data showing PFS at 12 months being about 80% (95% CI 60; 90%), benefit – risk is considered favourable, especially when put in the context of the totality of data. Altogether the following indication is supported: Venclyxto monotherapy is indicated for the treatment of CLL in the absence of 17p deletion or *TP53* mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.

Additional 60 patients will be enrolled in M14-032. This will enable confirmation of benefit – risk in the target population for the second part of the indication (specific obligation).

Safety data are non-comprehensive, especially as comparative safety data are missing. From this perspective the ongoing MURANO study where venetoclax is compared with bendamustine is considered key information to the benefit – risk (category 1).

The CHMP considered that Venclyxto falls under the scope of Article 2 of Commission Regulation (EC) No. 507/2006 as eligible for a Conditional Marketing Authorisation as it belongs to:

a) Medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) No 141/2000;

b) Medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases.

Furthermore, the requirements listed in Article 4 of Commission Regulation No 507/2006 apply to venetoclax on the basis of the following reasons:

a) The risk-benefit balance of the product is positive:

In patients with relapsed/refractory CLL in the presence of 17p deletion or TP53 mutations (Study M13-982) the overall response rate was 82.4 % in the safety expansion (SE) cohort, 74.8 % in the main cohort, and 77.2% in both cohorts; with CR of 15.7; 19.6% 18.4% respectively. Durability of response was long, resulting in PFS at 24 months of 69% (95% CI 60%; 77%) in the main cohort and PFS at 12 months in the SE cohort of 80% (95% CI 66%; 89%).

In subjects with CLL who were refractory or intolerant to treatment with either ibrutinib or idelalisib (study M14-032) responses were 69.8 % (IRC) and 67.4% (Inv) in ibrutinib failed cohort and 61.9% / 57.1% in the idelalisib failed cohort. Together with an acceptable safety-profile in patients in the proposed indications, the benefit-risk balance is considered positive.

b) It is likely that the applicant will be in a position to provide the comprehensive clinical data:

The applicant will provide further comprehensive clinical data to confirm efficacy and safety of venetoclax in the proposed indications. The updated M14-032 CSR will be submitted in 2018 (n=124) providing longer term efficacy and safety follow up for original cohort (n=64) and a second, 60 patient cohort has been added to the M14-032 protocol; of which 55 patients are currently enrolled. A complete 36 week response assessment for the second cohort is foreseen.

c) Fulfilment of unmet medical needs in the proposed indications:

There is no satisfactory treatment in post-BCRi CLL and there is no evidence-based standard of care in post-BCRi CLL, irrespective of mutation status. Further chemo-immunotherapy (CIT) in this population would be expected to have limited efficacy (Median PFS of 7 months to non-kinase inhibitor (Mato, 2015); Median PFS of 11 to 15 months for Bendamustine/Rituximab (BR); e.g. HELIOS).

d) The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required:

In view of the favourable benefit-risk profile, the high response rate including MRD responses, and acceptable safety profile, the immediate availability of Venclyxto on the market outweighs the risk inherent in the fact that additional data are still required.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus, is of the opinion that Venclyxto is not similar to Arzerra, Gazyvaro or Imbruvica within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Venclyxto in the following indications:

- Venclyxto monotherapy is indicated for the treatment of chronic lymphocytic leukaemia (CLL) in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor.
- Venclyxto monotherapy is indicated for the treatment of CLL in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.

is favourable and therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent

updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
PASS: In order to further confirm the overall safety profile and investigate the risk of Richter's syndrome/secondary primary malignancies, the MAH should submit the results of the MURANO study comparing venetoclax plus rituximab to bendamustine plus rituximab in patients with relapsed/refractory CLL	March 2018

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation:

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further confirm the efficacy and safety of venetoclax, the MAH should submit the clinical study report of study M14-032 investigating venetoclax in patients with chronic lymphocytic leukaemia relapsed after or refractory to treatment with B-cell receptor signalling pathway inhibitors.	March 2018

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that venetoclax is qualified as a new active substance.