Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Venetoclax

Proprietary Product Name: Venclexta

Sponsor: AbbVie Pty Ltd

November 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
AE	adverse event
AIHA	autoimmune hemolytic anaemia
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
aPTT	activated partial thromboplastin time
ASO-PCR	allele-specific oligonucleotide polymerase chain reaction
AST	aspartate aminotransferase
Bcl	B-cell lymphoma
BMI	body mass index
BR	bendamustine + rituximab
CD	cluster of differentiation
CI	confidence interval
CLL	chronic lymphocytic leukaemia
CTLS	clinical tumour lysis syndrome
CR	complete remission
CRi	complete remission with incomplete bone marrow recovery
CSR	clinical study report
CT	computed tomography
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DOR	duration of overall response
EC50	50% effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCCr	estimated creatinine clearance rate using Cockcroft-Gault formula
eCRF	electronic case report form
EFS	event-free survival

Abbreviation	Meaning
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	European Quality of Life 5 Dimensions-5 Levels Questionnaire
EQ VAS	European Quality of Life 5 Dimensions Visual Analogue Scale
ERIC	European Research Initiative in CLL
ESMO	European Society for Medical Oncology
FCR	fludarabine, cyclophosphamide, and rituximab
EU	European Union
FFPE	formalin-fixed, paraffin-embedded
FISH	fluorescence in situ hybridization
G-CSF	granulocyte-colony stimulating factor
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
IBM	ideal body mass
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IgVH	immunoglobulin variable region heavy chain
IHC	immunohistochemistry
IRC	Independent Review Committee
IRB	Institutional Review Board
ITP	idiopathic thrombocytopenic purpura
IUO/RUO	investigational use only/research use only
IV	intravenous
IWCLL	International Workshop for Chronic Lymphocytic Leukaemia

Abbreviation	Meaning
IxRS	Interactive Response System
LDH	lactate dehydrogenase
LDi	longest diameter
LSI	locus-specific identifier
LTLS	laboratory tumour lysis syndrome
LVEF	left ventricular ejection fraction
MDASI	MD Anderson Symptom Inventory
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MRI	magnetic resonance imaging
MUGA	multigated acquisition scan
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-WG	National Cancer Institute Working Group
NHL	non-Hodgkin's lymphoma
nPR	nodular partial remission
NPT	non-protocol anti-lymphoma therapy
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PET	positron emission tomography
PFS	progression-free survival
PG	pharmacogenetic(s)
PK	pharmacokinetic(s)
PR	partial remission
PR-i	CR except for incomplete recovery of blood counts
PR-nod	nodular partial response
PT	prothrombin time
QA	quality assurance
QC	quality control
QD	once daily
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-CLL16	Quality of Life Questionnaire-Chronic Lymphocytic Leukaemia 16

Abbreviation	Meaning
QoL	quality of life
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SLL	small lymphocytic lymphoma
SMQ	standardized MedDRA query
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TLS	tumour lysis syndrome
TTNT	time to next anti-CLL treatment
TTP	time to progression
ULN	upper limit of normal
USA	United States of America
WBC	white blood cell

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	15 December 2016
Date of entry onto ARTG	5 January 2017
Active ingredient(s):	Venetoclax
Product name(s):	Venclexta
Sponsor's name and address:	AbbVie Pty Ltd 241 O'Riordan St, Mascott NSW 2020
Dose form(s):	Film-coated tablets
Strength(s):	10 mg, 50 mg and 100 mg
Container(s):	Plastic bottles and blister trays (with plug-assist)
Pack size(s):	Starter pack for up-titration –week 1 (14 times 10 mg tablets), week 2 (7 times 50 mg tablets), week 3 (7 times 100 mg tablets), and week 4 (14 times 100 mg tablets) The 100mg tablet strength is supplied as a blister pack (112 tablets) and in HDPE bottles (120 tablets)
Approved therapeutic use:	*Venclexta is indicated for the treatment of:* · *patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) with 17p deletion, or* · *patients with relapsed or refractory CLL for whom there are no other suitable treatment options.* *Note to indications. The indications are approved based on overall response rates. Duration of response and improvements in overall survival.*
Route(s) of administration:	Oral (PO)
Dosage:	The starting dose of Venclexta is 20 mg once daily for 7 days. The Venclexta dose must be administered according to a weekly dose titration schedule to the recommended daily dose of 400 mg over a period of 5 weeks as shown in Table 6. [see Attachment 1 PI]. The 5-week dose titration schedule is designed to gradually reduce tumour burden (debulking) and decrease the risk of TLS.

ARTG number (s): 267443, 267441, 267442, 267445 and 267444

Product background

This AusPAR describes the application by the sponsor to register Venclexta (venetoclax) a new chemical entity, for the following indications:

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

This indication was modified by the clinical evaluator to:

> *Venclexta is indicated for the treatment of patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion.*

This was subsequently amended by the sponsor and the Delegate to the following:

1. *Venclexta is indicated for the treatment of relapsed or refractory chronic lymphocytic leukaemia (CLL) with 17p deletion.*
2. *Venclexta is indicated for the treatment of patients with relapsed or refractory CLL without the 17p deletion for whom there are no suitable treatment options.*

Note to indication. These indications are approved based on overall response rates. Duration of response and improvements in overall survival or health-related quality of life have not been established.

The proposed dosing regimen involves a five week dose escalation starting at 20 mg/day with weekly progression to 50, 100 and 200 mg/day until the recommended dose of 400 mg/day orally (PO) is reached. Treatment is intended to continue until disease progression or unacceptable toxicity occurs. See Table 6 in PI for further details (Attachment 1).

The whole one month starter pack is proposed to be supplied complete, with recommendations for blood tests and clinical assessment before up- titrating contained in the PI. Treatment should continue until disease progression or unacceptable toxicity. Dose modifications are recommended.

Venetoclax is a selective inhibitor of the B-cell leukaemia 2 (Bcl-2) protein which is an anti-apoptotic protein. Overexpression of Bcl-2 has been demonstrated in CLL cells, mediating tumour cell survival and has been associated with chemotherapeutic resistance.

CLL is one of the chronic lymphoproliferative disorders and is characterised by a progressive accumulation of functionally incompetent lymphocytes, which are usually monoclonal in origin. In Australia, the average of age of onset is 70 years of age, with a male preponderance. While some patient subsets have survival rates that are similar to the normal population, others who present with early stage disease and poor-risk prognostic markers (for example, 17p deletion, 11q deletion, TP53 mutations, CD38 positivity, un-mutated segments of the immunoglobulin heavy chain variable [IGHV] genes) have a less favourable prognosis. Prior to the availability of targeted agents, patients with deletion of 17p were at high risk of either not responding to initial chemotherapy or chemo-immunotherapy treatment or relapsing soon after achieving remission.

In general, therapy is not offered to patients in early stage with poor risk disease outside a clinical trial. Therapy is offered to all CLL patients regardless of risk when needed according to the International Workshop on Chronic Lymphocytic Leukaemia (IwCLL) guidelines to patients with early stage and poor risk disease (usually in a clinical trial if

possible), symptomatic CLL or advanced stage Small lymphocytic lymphoma (SLL) with the goals of ameliorating symptoms and improving progression-free and overall survival. With the possible exception of allogeneic hematopoietic cell transplantation, CLL cannot be cured by current treatment options.

The currently approved therapies in Australia for patients with a specific indication for CLL harbouring 17p deletion are:

Idelalisib

> *Zydelig is indicated in combination with rituximab for the treatment of patients with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL), including patients with 17p deletion or TP53 mutation, upon relapse after at least one prior therapy in patients for whom chemoimmunotherapy is not considered suitable.*
>
> *Zydelig is not recommended for first-line treatment of CLL/SLL.*
>
> *Zydelig is indicated as monotherapy for the treatment of patients with follicular lymphoma which is refractory to at least two prior systemic therapies.*

Ibrutinib

Imbruvica is indicated for the treatment of

- *patients with CLL/SLL who have received at least one prior therapy or as first line in patients with CLL with 17p deletion*
- *patients with MCL who have received at least one prior therapy*

The approvals for idelalisib and ibrutinib in patients with CLL were based upon randomised clinical trial with progression-free survival as the primary end-point.

With each CLL relapse, the number of remaining therapeutic options is reduced. Despite the availability of these two recently registered products, and the uptake of their use, resistance to each therapy has been reported. This demonstrates an ongoing need for additional therapeutic options particularly for those with 17p deletion.[1]

For Australian patients with 17p deletion, the approved first line therapy is ibrutinib, or idelalisib in those not suitable for chemoimmunotherapy. For those patients not suitable for chemoimmunotherapy, the optimal treatment of the two options has not yet been resolved.

Other medicines registered for use in CLL do not contain specific indications or contraindications for use in patients with 17p deletion.

The following TGA adopted European Union (EU) guideline provided guidance for evaluation of this submission:

- Guideline on the evaluation of anticancer medicinal products in man. (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/0 1/WC500137128.pdf)

[1] Woyach, J et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. NEJM 2014; 370:2286-2294

Sorensen, R et al. Investigation of the Mechanism of Idelalisib Resistance in the Follicular Lymphoma WSU-Fsccl Cell Line. Blood 2015; 126:2482

Regulatory status

This is an application for a new chemical entity. The initial registration on the Australian Register of Therapeutic Goods (ARTG) occurred on the 5 January 2017.

Similar applications have been approved in the European Union (EU) and the USA (Table 1) and is under consideration in Canada (December 2015, filed for consideration under the Notice of Compliance with Conditions policy). The proposed indication for Canada and that approved by the FDA is similar to that being sought in Australia. Venetoclax was approved by the US FDA under priority review with a break-through designation for the indication in patients with 17p deletion.

Table 1: International regulatory status

Country	Submission Date	Status	Marketed indication (approved or requested)
USA	29 October 2015	Accelerated (conditional) approval April 11, 2016	Approved under accelerated approval for the treatment of patients with chronic lymphocytic leukemia with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
EU	13 November 2015	CHMP recommendation 17 October 2016	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.

There are some differences in the EU approved indication which is shown below. The differences are underlined and highlighted:

> *Treatment of adult patients with chronic lymphocytic leukaemia in the presence of 17p deletion or TP53 mutations.*

The wording of the condition in the Accelerated Approval letter given by the FDA is:

- PMR # 3068-1: Submit the complete final report and data from ongoing trial GO28667, a randomized, Phase 3 trial comparing Venclexta (venetoclax) and rituximab with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia (CLL), including CLL with deletion 17p. (Trial due for completion May 2018).

Submission of additional post-marketing studies for evaluation has also been mandated by the FDA:

- PMR # 3068-2: Evaluate the effect of hepatic impairment on the pharmacokinetics and safety of Venclexta (venetoclax) compared to subjects with normal hepatic function. Submit a complete final report with all supporting datasets for trial M15-342 entitled, 'A Study to Evaluate the Safety and Pharmacokinetics of a Single Dose of Venetoclax in Female Subjects with Mild, Moderate, or Severe Hepatic Impairment.' (Trial due for completion March 2017)
- PMR # 3068-3: Evaluate the effect of Venclexta (venetoclax) co-administration on pharmacokinetics of a probe substrate of P-gp. Submit a complete final trial report with all supporting datasets. (Trial due for completion November 2016).

Of note, the recommendation of the CHMP for Marketing Authorisation approval of 17 October 2016 additionally recommends that venetoclax be prescribed by physicians experienced in the treatment of CLL and the use of anticancer medicines.

Product Information

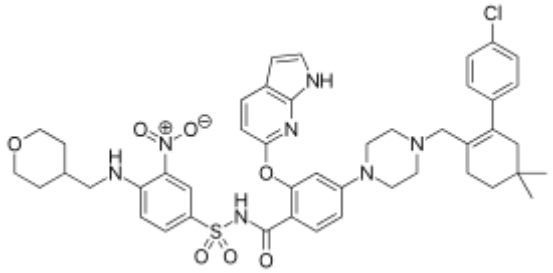
The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Drug substance (active ingredient)

Venetoclax (chemical structure in Figure 1 below) is obtained as a single structural isomer that contains no stereogenic centres and is achiral. The drug substance is obtained as a crystalline powder. No polymorphs have been identified. The drug substance is slightly soluble in pH 1 and 12.9 solutions but practically insoluble at pH 4 to 7.4. It is very soluble in methylene chloride and vinylpyrrolidone dimer. An n-octanol/pH 7.4 buffer partition coefficient of 5.5 was determined experimentally.

Figure 1: Chemical structure of venetoclax



The drug substance is produced by chemical synthesis in four stages. The manufacturing process description includes process parameters and in-process controls for all steps.

The drug substance specification adequately controls identification, assay, related substances, residual solvents, water content, residue on ignition and microbiological aspects. Particle size distribution is not controlled in the drug substance. The drug substance particle size has been shown not to affect this step.

Drug product

The proposed tablets are round (10 mg) or oblong (50 and 100 mg), biconvex, pale-yellow (10 and 100 mg) or beige (50 mg), film-coated tablets debossed with 'V' on one side and the strength on the other, with different colourants in the film-coating.

Due to the low bioavailability of the crystalline drug substance it is formulated as an amorphous solid dispersion with copovidone, polysorbate and silica. The amorphous solution is then transferred to a separate manufacturing site where it is milled and blended with calcium phosphate, silica and sodium stearyl fumarate prior to compression, film-coating and packaging. The amorphous solid dispersion was shown to be physically stable, with no crystallisation observed after 6 months.

The finished product specification includes tests and limits for appearance, identification, assay, uniformity of dosage units, water content, dissolution, and degradation products. The sponsor has specified two degradants, which lie outside the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) qualification limits but that have been justified toxicologically.

The proposed routine dissolution method operates under sink conditions. The discriminatory power of the dissolution method has been demonstrated.

Stability data were provided to support the proposed shelf life of the drug product.

The proposed shelf life for the finished product is 24 months at 30°C.

Stability data confirms that bottles are suitable for use as a one month supply.

Biopharmaceutics

A relative bioavailability study (Study M14-253) and a bioequivalence study of tablets manufactured at the development and commercial sites and effect of food (Study M15-101) were conducted.

Study M14-253

This study was an open-label, randomised, single-dose, two-period, crossover study conducted to assess the relative bioavailability of uncoated and film-coated venetoclax 50 mg tablets in healthy female subjects under fed conditions. The investigators concluded that the uncoated and film-coated tablets were bioequivalent. This study was not evaluated in full as the uncoated tablets were only used in Phase I and II studies and the formulation of the film-coated tablets used in the Phase III studies is identical to that proposed for registration.

Study M15-101

This study was an open-label, randomised, single-dose, four-period, complete-crossover study in 24 subjects, conducted to compare the bioavailability of film-coated venetoclax 100 mg tablets manufactured at the site for commercial manufacture (1) to that of film-coated venetoclax 100 mg tablets manufactured at the site for formulation (2) and manufacturing process development under fed (low-fat) conditions and to assess the effect of food (low-fat or high-fat) on the pharmacokinetics of a 100 mg dose of venetoclax compared to fasting conditions.

The study reported the following pharmacokinetic parameters and statistical analyses for test (1) and reference (2):

Peak plasma concentration (C_{max}):

0.499 µg/mL (Test): 0.466 µg/mL (Reference)

Area under the concentration versus time curve to time t (AUC_t):

6.774 µg.h/mL (Test): 6.254 µg.h/mL (Reference)

Area under the concentration versus time curve from time zero to infinity (AUC_{inf}):

7.066 µg.h/mL (Test): 6.523 µg.h/mL (Reference)

The results of the study support the conclusions that plasma exposures achieved after administration of venetoclax 100 mg tablets manufactured at the development and commercial sites were very similar but not bioequivalent, as the upper bounds of the 90% confidence intervals were slightly above 125.0%, and that administration of venetoclax 100 mg tablets with a low or high fat meal increased plasma exposure approximately 3.4 and 5.2 fold respectively when compared to administration under fasting conditions; with a high-fat meal increasing exposure approximately 1.5 fold when compared to administration with a low-fat meal. The clinical significance of these results was considered a matter for the clinical evaluator to assess.

Justification for non-supply of bioavailability/bioequivalence data

The sponsor has provided a justification for not providing an absolute bioavailability study. The sponsor stated that an absolute bioavailability study could not be justified on safety grounds as it would require a strong organic solvent for the formulation of an intravenous solution and sufficient information on the pharmacokinetics of venetoclax are already available from preclinical and clinical studies.

Quality summary and conclusions

No significant issues were identified in the chemistry and biopharmaceutical assessment of the submission and as such approval is recommended from a chemistry and quality perspective.

III. Nonclinical findings

Introduction

Venetoclax is the first drug in its pharmacological class of Bcl-2 inhibitors. The quality of the nonclinical submission4 was generally good with all pivotal safety-related and toxicity studies conducted according to Good Laboratory Practice (GLP).

Study designs were sound, used appropriate animal species and sufficient group numbers, and in general adhered to the appropriate guidelines where relevant (that is, ICH S9[2], S2(R1)[3] and S8[4]).

To address the toxicological qualification of the disproportionate human metabolite (M27) of venetoclax, the sponsor advised that they were in the process of finalising a 4 week GLP-compliant toxicity study in mice with M27 that was to be submitted to the TGA when available. This was not available at the time of completion of the nonclinical evaluation report

[2] ICHS9 Nonclinical Evaluation For Anticancer Pharmaceuticals
[3] Guidance for Industry S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use
[4] S8 Immunotoxicity Studies For Human Pharmaceuticals

Pharmacology

Primary pharmacology

Venetoclax is an inhibitor of the anti-apoptotic protein, Bcl-2. Venetoclax bound preferentially to Bcl-2 compared to other Bcl family members (Ki of <0.01 nM for Bcl-2 compared to 48 nM for Bcl-XL, 245 nM for Bcl-w and >400 nM for Mcl-1). In vitro, venetoclax inhibited the growth of cells dependent on Bcl-2 for survival with a concentration that gives half-maximal response (EC_{50}) of 4 nM and disrupted the Bcl-2-BIM complex (releasing pro-apoptotic BIM) with a 50% inhibitory concentration (IC_{50}) of 3 nM. It had low inhibitory activity against cells dependent on Bcl-XL (EC_{50} 261 nM). Similarly, venetoclax concentration-dependently activated apoptotic pathways in tumour cells in vitro. Venetoclax inhibited the growth of a variety of leukaemia cell lines in vitro, with the mean IC_{50} for CLL cell lines approximately 6 nM. EC_{50} values were generally lower for leukaemia and lymphoma cells lines bearing the t(14;18) translocation. In summary, venetoclax inhibited Bcl-2 and promoted apoptosis at concentrations well below those expected clinically.[5]

The sensitivity of tumour cell lines to venetoclax correlated to their expression of Bcl-2 but not Bcl XL. Co-culture with venetoclax and bortezomib had a synergistic effect in inhibiting tumour cell growth. The development of venetoclax resistance was investigated in vitro. Resistant cell lines commonly had altered expression of anti-apoptotic Bcl-2 family members, including decreased expression of Bcl-2 and apoptosis effectors BIM and BAX, and increased expression of Bcl-XL and Mcl-1.

The major human metabolite M27 was also shown to bind Bcl-2 with a Ki value of 2.2 nM (>220 fold lower potency than venetoclax). However, M27 was ineffective in inhibiting the growth of Bcl-2-dependent ALL tumour cells in culture.

In wild type mice, venetoclax reduced total lymphocytes, B cells, helper T cells and cytotoxic T cells at exposures 2.7 times the clinical AUC. Similar effects were reported at subclinical exposures in dogs and mice in the repeat dose toxicity studies. In tumour xenograft models, venetoclax was effective both alone and in combination with other anti-cancer drugs in inhibiting the growth of various lymphoma and leukaemia tumours at subclinical exposures. Combination therapies were generally more effective than either agent alone. Together, the primary pharmacology data support the proposed indication.

Secondary pharmacodynamics and safety pharmacology

Secondary pharmacology studies found venetoclax bound to prostacyclin (Ki 0.8 μM, IC_{50} 1.4 μM), peripheral benzodiazepine (Ki 0.4 μM, IC_{50} 0.4 μM) and serotonin-5a (Ki 0.4 μM, IC_{50} 0.7 μM). Interactions are not expected clinically as the unbound C_{max} is estimated to be <2 nM. In addition, M27 inhibited delta-opioid receptors (Ki 0.8 μM, IC_{50} 1.4 μM) but the EC_{50} was estimated to be >10 μM in a functional assay. This is not expected to have any clinical significance.

Specialised safety pharmacology studies covered the central nervous system (CNS), cardiovascular and respiratory systems. There was no effect of venetoclax on behaviour in mice at doses up to 600 mg/kg (relative exposure [RE] 4.5[6] based on C_{max}) or rats at doses

[5] The clinical plasma C_{max} was 2.1 μg/mL (2.4 μM). In vitro experiments were performed in the presence of serum, and therefore the high plasma protein binding is expected to be present in the in vitro experiments, allowing comparison of total concentration and total plasma Cmax.

[6] 4.5 times higher than the expected C_{max} in humans

up to 100 mg/kg PO (RE of 1.8).[7] Similarly, adverse CNS signs were not reported in dogs in the repeat dose toxicity studies which achieved relative venetoclax exposure of >40 times that expected in humans.[8] Venetoclax inhibited potassium (hERG K+) channels, but with an estimated IC_{50} of 11.5 μM, which exceeds the total clinical C_{max} by > 5 times and is unlikely to be clinically relevant given the very high plasma protein binding. Small effects on electrocardiogram (ECG) parameters were observed in anaesthetised dogs given ≥ 3.3 mg/kg IV venetoclax (RE 8 based on C_{max}). In contrast, there were no treatment-related ECG abnormalities in conscious dogs following a single or repeated dose of ≤ 150 mg/kg PO (RE 16 times based on C_{max} on Day 28 of 4 week repeat dose study in dog and on clinical C_{max}). Respiratory function was not affected by ≤ 600 mg/kg PO venetoclax in mice (RE 4.5 times).

Pharmacokinetics

Early studies identified the formation of insoluble solvates in lipid formulations which resulted in high variability in exposure in animals. Amorphous solid dispersion formulations were developed to overcome solubility issues and were used in the pivotal repeat dose toxicity studies. The pharmacokinetics discussion below focuses on these formulations.

In vitro, venetoclax was shown to have moderate permeability across intestinal cell monolayers. In vivo, absorption rate of venetoclax was variable in animals (time to C_{max} (T_{max}) 1 to 6 h in mice, 3 to 12 h in rats and 2 to 16 h in dogs) but was more consistent in humans (5 to 8 h). Bioavailability was low in mice (27%), rats (12%) and dogs (15 to 28%). Oral bioavailability data were not available in humans. Exposure was generally less than dose-proportional and at higher doses exposure appeared to plateau in dogs. In mice, exposure to venetoclax decreased with repeated dosing whereas in dogs venetoclax appeared to accumulate over time. There was no consistent effect of gender in mice or dogs. Plasma half-life was long in dogs approximately 14 h), but shorter in mice approximately 3 h) and rats (approximately 8 h), compared with approximately 26 h in humans.

Venetoclax was highly bound to plasma proteins in all species (>99.99%), as was the major human metabolite, M27. Venetoclax did not preferentially partition into red blood cells. The volume of distribution was less than total body water in mice, dogs and humans, indicating limited tissue distribution. Studies of radiolabelled venetoclax showed high levels in bile and liver, with moderate exposure in lymph nodes, adrenal glands and kidney. Distribution to other tissues generally reflected plasma concentrations. Distribution to the brain and reproductive organs was low.

Venetoclax metabolites were formed mainly by oxidation, sulfation and reduction, or a combination of these processes. Venetoclax was relatively stable in vitro but the metabolites formed were similar between mice, dogs and humans, although additional human metabolites were reported. In animals, unchanged venetoclax was the dominant circulating species (86 to 95%). In humans there was a disproportionate major metabolite, M27, which was present at approximately 44% the level of venetoclax. There were no other major plasma metabolites in humans or animals. No M27 was detected in mouse, rat or dog plasma after a single dose of venetoclax. Very low exposure to M27 was demonstrated in dogs and mice following repeated (5 day) dosing with high doses of venetoclax, with M27 present at <1% the level of venetoclax. M27 was not detected in the

[7] Relative exposure values extrapolated from Cmax in female mice that received 600 mg/kg PO on day 1 of dosing in the 4-week toxicity study (R&D/10/342), and in male rats that received 100 mg/kg PO in the pharmacokinetic study (Drug Metabolism Memo No. 04), dosed with venetoclax in the same or similar formulations as in the safety pharmacology studies.

[8] Based on a C_{max} value of 90 μg/mL in male dogs on Day 6 of Study R&D/09/1105

plasma from the pivotal dog repeat dose toxicity study. In vitro studies indicated metabolism of venetoclax and M27 was mainly by cytochrome P450 (CYP) isozyme CYP3A4, with a lesser contribution from CYP3A5. Additional CYP isoforms were also capable of metabolising M27.

Excretion of venetoclax was via the faeces in mice, rats dogs and humans, with renal excretion accounting for <1% of the administered dose. Biliary excretion was demonstrated in bile duct-cannulated rats and accounted for 93% of an IV dose. In rat bile, venetoclax was excreted mainly as metabolites. Higher levels of unchanged venetoclax were observed in mouse, dog and human faeces (approximately 20 to 50%). However, as oral dosing was used and a large fraction of the radioactivity (>93%) was recovered from the bile of intravenously dosed rats, unchanged venetoclax recovered in faeces was most likely due to poor absorption.

In summary, the absorption of venetoclax was variable in animals but moderate exposure was achieved that increased with increasing doses. Distribution was limited in animals and humans which is consistent with the very high level of protein binding. The plasma metabolite profile differed significantly between animals and humans with the relative absence of M27 in animal plasma. Repeat dose toxicity studies with M27 were not submitted to overcome this significant difference. Overall, the similarity in pharmacokinetic profile in animals and humans was qualitatively similar except for the difference in M27 exposure. This difference is acceptable as the proposed indication is for the treatment of advanced cancer.[2]

Pharmacokinetic drug interactions[9]

Transporter interactions

In vitro and in vivo data demonstrated that venetoclax and its major human metabolite M27 were both substrates for P glycoprotein and BCRP. In vitro, venetoclax and M27 inhibited P-glycoprotein and breast cancer resistance protein BCRP) in vesicles, but not MDCKII cells, with IC_{50} values of approximately 0.8 µM for both venetoclax and M27 against P-gp and 0.1 and 1.5 µM, respectively, against BCRP in inverted vesicular preparations. However, in MDCKII cells expressing P-gp or BCRP, the IC_{50} of venetoclax was > 85 µM. In response to a TGA query concerning the 100 to 600 fold lower IC_{50} values for vesicular preparations compared to intact cells, the sponsor referred to venetoclax accessibility due to its low permeability, such that venetoclax directly interacts with P-glycoprotein and BCRP in the inside-out vesicular membranes, whereas access to these transporters in intact cells is likely hampered by low cell permeability. Nevertheless, intestinal inhibition of both P glycoprotein and BCRP is predicted, based on maximal intestinal venetoclax concentrations (400 mg/0.25 L = 1.8 mM). However, systemic effects on P-glycoprotein and BCRP are unlikely to be clinically significant due to very high protein binding by both species (>99%).

[9] The assessment of pharmacokinetic drug interactions is based on the following:
- For venetoclax – molecular weight, 868.44; dose, 400 mg; C_{max}, 2.4 µM (total); free fraction, 1% (based on the EMA drug-drug interaction guideline a 1% free fraction is assumed when binding is ≥99%); intestinal volume, 0.25 L; absorption rate constant, 0.003 min-1 [3.76 24h-1 from population PK study]; kdeg for CYP3A, 0.0005 min-1
- For M27 – molecular weight, 882.4; C_{max} 0.8 µM; free fraction 1% (as above – plasma protein binding was ≥99%)
- for intestinal CYP (CYP3A) and intestinal transporters (P-glycoprotein and BCRP): if the IC50 is ≤0.1-fold the intestinal concentration, an in vivo interaction is considered possible
- for systemic CYP, renal uptake and efflux transporters, and hepatic efflux transporters (OAT1, OAT3, OCT2, MRP2, BCRP, P-glycoprotein, MATE1 and MATE2K): if the IC50 is ≤50-fold the unbound clinical C_{max}, an in vivo interaction is considered possible
- for hepatic uptake transporters (OCT1, OATP1B1 and OATP1B3): if the IC50 is ≤25-fold the unbound hepatic inlet concentration, an in vivo interaction is considered possible.

Venetoclax inhibited the hepatic transporter OATP1B1 with IC_{50} values 3 to 14 μM in the absence and presence of 4% bovine serum albumin (BSA). It also inhibited OATP1B3 and OAT3 with IC_{50} values of ≥ 12 in the absence BSA but no inhibition was seen in the presence of 4% BSA. Plasma C_{max} was 2.4 μM, and this coupled with high plasma protein binding and low absorption indicated that clinical inhibition of OATP1B3 and OAT3 is unlikely. Interaction of venetoclax with other transporters was also investigated with no clinically relevant inhibition found.

The interaction of M27 with hepatic and renal transporters was also investigated in vitro. M27 also inhibited OATP1B1, OATP1B3 and OAT3 with IC_{50} values of 0.1–0.3 μM. The IC_{50} values increased to ≥ 15 μM in the presence of 4% BSA. The clinical plasma C_{max} for M27 was 0.8 μM, with strong protein binding also reported (≥ 99%). Overall, these data indicate that inhibition of these transporters by M27 is unlikely to be clinically relevant.

Enzyme interactions

Venetoclax is mainly metabolised by CYP3A4. Thus, CYP3A4 inhibitors and inducers may increase and decrease, respectively, the plasma venetoclax concentration in patients. This has been confirmed by clinical studies.

Venetoclax and M27 inhibited CYP isoforms 2C8 and 2C9 with IC_{50} values of 0.8 μM for 2C8 and 0.1 to 0.3 μM for 2C9. The IC_{50} values were markedly increased to >50 μM when inhibition studies were performed in the presence of 4% BSA. M27 was also a weak inhibitor of CYP3A4 in the absence of BSA (IC_{50} of 6 μM), but the IC_{50} values increased to >300 μM in the presence of BSA. Venetoclax was a time-dependent inhibitor of CYP2B6, but only following exposure to high concentrations (50 μM). Similarly, M27 was a time dependent inhibitor of CYPs 2B6 and 3A4 but only modest inhibition (11 to 40%) was observed at 10 μM. Overall, these data do not indicate that venetoclax is likely to cause significant CYP inhibition at the anticipated clinical exposures.

Venetoclax and M27 inhibited UDP glucuronosyltransferase 1A1 (UGT1A1) with IC_{50} values of approximately 0.2 μM, with the effects of plasma protein not investigated. Some clinical inhibition of this UGT enzyme is considered possible, but unlikely given the very high levels of plasma protein binding. M27 also inhibited UGT1A4 and 2B7 with IC_{50} values of 7.5 and 0.7 μM. Inhibition of these enzymes is considered unlikely based on the predicted clinical exposure to unbound M27.

There was no clear evidence of venetoclax inducing the expression of CYPs 1A2, 2B6 or 3A4 in human hepatocytes exposed to ≤ 50 μM venetoclax for 2 days in the presence of 4% BSA. The duration of these experiments was less than the recommended 3 day duration[10] without clear justification. However, induction was not observed even at concentrations that exceeded the anticipated clinical C_{max} by >20 times. Therefore, induction of CYP1A2, 2B6 and 3A4 enzymes by venetoclax is not anticipated based on the proposed clinical use.

Induction of CYP enzyme expression (CYP1A2, 2B6, 2C8, 2C9, 2C19 and 3A4) was also investigated for M27. In the presence of BSA, M27 induced CYP3A4 in a concentration-dependent manner from 3 μM with an EC_{50} of approximately17 μM. Modest induction of CYP2B6 was also reported at 30 μM M27. Clinically, M27 is unlikely to induce CYP3A4 to an extent that would cause drug-drug interactions.

[10] EMA Guideline on the investigation of drug interactions.

Toxicology

Acute toxicity

Dedicated single-dose toxicity studies were not conducted, with the exception of a single dose dog study which is discussed in the Immunotoxicity section below. In repeat dose-studies of ≥ 2 weeks duration, the maximum non-lethal dose was 500 mg/kg/day in CD 1 mice, 600 mg/kg/day in CByB6F1 mice, 400 mg/kg/day in SD rats and 150 mg/kg/day in beagle dogs. These doses were associated with relative exposures of 3 to 9 times the clinical C_{max} on the first day of dosing. However, as acute mortality was not observed in these studies the maximum single non-lethal dose may be higher.

Repeat dose toxicity

Studies of up to 26 weeks duration were conducted in mice, 13 weeks in rats and 9 months in dogs. All studies using single daily oral dosing which is consistent with the intended clinical use. The duration, design and conduct of studies were consistent with the relevant guidelines.[11] Mice were used as the rodent species for pivotal repeat dose toxicity studies. The studies conducted in rats were dose-range finding studies for future carcinogenicity studies and included a full investigation of clinical and anatomic pathology. Mice were selected as the main rodent species due to difficulties in obtaining dose-related exposure to venetoclax in rats, even with the use of twice daily dosing.

Relative exposure

Exposure ratios have been calculated based on animal: human plasma $AUC_{0-24\,h}$. Human reference values are from Clinical Study M12-175 and represent the steady state. The AUC data used for animals are from the last sampling occasion. The mean values for male and female values were used except for the high dose group in the 39 week repeat dose dog study in which exposure was approximately 4 times higher in female compared to male dogs. Total plasma AUC values were used as the plasma protein binding was very high in all species including humans (>99.99%).

Table 2: Relative exposure in repeat dose toxicity studies

Species	Study duration [Study no.]	Dose mg/kg/day	AUC0–24 h^ µg·h/mL	Exposure ratio#
Mouse (CD-1)	26 weeks Study R&D/12/522	15	2.7	0.08
		50	7.3	0.2
		300	26	0.8
Rat (SD)	13 weeks Study R&D/14/0959	8 (♀)	17	0.5
		15 (♂)/30 (♀)	11/33	0.3/1
		150 (♂/♀)	26/83	0.8/2.5
		400 (♂/♀)	44/75	1.3/2.3
Dog (Beagle)	4 weeks Study R&D/10/224	5	31	1.9
		50	472	14
		150	572	17
	9 months Study R&D/12/384	2	17	0.5
		6	52	1.6
		20 (♂/♀)	32/139	1.0/4.2
Human (patients)	steady state Study M12-175	[400 mg]	32.8	–

[11] ICH guideline M3(R2) and EMA guideline on repeated dose toxicity studies (CPMP/SWP/1042/99 Rev1)

= animal: human plasma AUC_{0-24h}; ^ = data are for the sexes combined at the last sampling occasion except where indicated

Major toxicities

The major target organs for venetoclax were the testes and haematology system. Venetoclax also decreased pigment in the hair follicle bulbs in dogs. Some effects were also seen in the gallbladder, liver, pancreas, stomach and kidneys.

Adverse effects were observed in the male reproductive organs in dogs following repeated oral dosing with ≥ 2 mg/kg/day venetoclax (relative exposure [RE] of ≥ 0.5 times). Moderate to severe atrophy and/or degeneration of the seminiferous tubules was observed in the testes of all treated male dogs. This led to severe oligospermia and/or reductions in spermatogonia, which progressed to severely reduced germ cell numbers after a 4 week recovery period. These changes were bilateral and associated with reduced testes weight. There was no clear relationship to dose but this may be due to high sensitivity to these effects as they were severe at all dose levels. Similar effects were generally not observed in mice and rats except for moderate oligospermia in the epididymides of one mouse that received 300 mg/kg/day PO venetoclax for 6 months (RE 0.8 times). The Bcl-2 family of proteins are involved in the regulation of spermatogenesis, with expression of Bcl-2 family members (including Bcl-2 itself) shown in human testis.[12] The observed adverse effects in testis are likely to have a pharmacological basis. These findings are of clinical concern given their severity and incidence at low relative exposures.

Haematological effects were pharmacological and observed in all species at all doses. The expected effect on circulating white blood cells and in particular lymphocytes, were observed and occurred as little as two days after the initiation of dosing. Lymphocyte phenotyping in dogs demonstrated the greatest effects on mature B cells, with reductions of ≤ 75% after 2 days dosing and >90% after as little as 2 weeks dosing. Total lymphocyte and T cell populations (mature, helper and cytotoxic T cells) were also decreased but not as severely. Lymphocyte numbers increased following the cessation of dosing but the cell counts for total lymphocytes, mature B and T cells as well as T helper cells were not restored to baseline levels after a 2 week dosing period followed by a 4 month recovery period.

Lymphoid organs also showed expected pharmacological effects including depletion of lymphocytes in lymph nodes, spleen, Gut-associated lymphoid tissue (GALT) and thymus from doses of 15 mg/kg/day in mice, at 8 mg/kg/day in rats and 2 mg/kg/day in dogs (RE of <1). These effects were dose-dependent and showed evidence of reversibility in mice and dogs (reversibility not studied in rats), but appeared to take longer to resolve in dogs compared to mice.

Venetoclax affected erythrocyte parameters in mice and dogs at doses ≥ 50 mg/kg/day (RE of 0.2 times and 14 times, respectively) and in rats at ≥ 30 mg/kg/day (RE of 1 times). Haemoglobin and haematocrit decreased, generally by a greater magnitude than the reduction in red blood cell numbers. Mean corpuscular volume and mean corpuscular haemoglobin also decreased and red cell distribution width increased. In mice and female rats, reticulocytes were commonly increased (more so following shorter duration of treatment), whereas in dogs reticulocytes were either unchanged or decreased. The effect of venetoclax on erythrocyte parameters is likely a pharmacology effect associated with inhibition of Bcl-XL and/or Bcl-2. The EC_{50} for Bcl-XL was 261 nM (approximately 0.2

[12] Sugiyama N, *et al*. Bcl-2 Inhibits Apoptosis of Spermatogonia and Growth of Spermatogonial Stem Cells in a Cell-Intrinsic Manner. *Mol Reprod Dev.* 2001; 58: 30-8.
Oldereid NB, *et al*. Expression of Bcl-2 family proteins and spontaneous apoptosis in normal human testis. *Mol Hum Reprod.* 2001; 7: 403-8.

µg/mL), which is well below the plasma C_{max} values of 1 to 2 µg/mL and 10 to 34 µg/mL reported in mice and dogs that had received 50 mg/kg/day venetoclax and approximately 2 µg/mL in rats at 30 mg/kg/day. Both Bcl-XL and Bcl-2 are involved in the survival and maturation of red blood cells, in part through their interactions with erythropoietin[13] and Bcl-2 is expressed in all haematopoietic precursor cells in bone marrow.[14] In addition, Bcl-XL is also required for haemoglobin synthesis.[15] Erythrocyte morphological abnormalities were observed in rats (particularly in females) and included poikilocytosis, anisocytosis, and basophilic stippling at all doses in the 13 week study. Clinically, some effect on erythrocytes is likely given the relatively low exposure margin in mice and pharmacological mechanism of action. In the nonclinical studies the magnitude of these changes was generally small and therefore similar effects clinically may not be severe. Platelet counts were unaffected except for small increases in male mice at 300 mg/kg/day in the 6 month study, female rats at ≥ 30 mg/kg/day and in short term studies in dogs, although Bcl-2 is highly expressed in megakaryocytes.[14]

Progressive white discolouration of the hair was observed in all dogs that received ≥ 6 mg/kg/day PO venetoclax after at least 13 weeks of dosing (RE 1 to 4 times). Pigment in the hair follicle bulbs was also reduced in a dose-related manner from 2 mg/kg/day (RE 0.5 times). The reversibility of this finding was not investigated as it did not develop in the short-term dog studies which included recovery periods, despite higher dose levels. This finding is considered to be pharmacological as Bcl-2 is involved in the development and survival of melanocyte stem cells and Bcl-2 null mice are known to be hypopigmented.[16]

Single cell necrosis was observed in epithelial tissues (stomach, gallbladder, pancreas, thymus, GALT, prostate and epididymides) in dogs that received ≥ 2 mg/kg/day PO venetoclax (RE ≥ 0.5 times). These findings were generally of minimal severity, with mild severity in the pylorus stomach in the 39 week dog study. Single cell necrosis resolved in all tissues after a 4 week non-dosing period, except in the prostate and epididymides. Similar findings have been reported in nonclinical studies of a pan-Cyclin Dependent Kinase (CDK) inhibitor.[17] CDK regulates Bcl-2 function by phosphorylation.[18] Therefore, it is plausible that the observed single cell necrosis is related to the pharmacological effects of venetoclax.

There were no signals of renal and hepatic toxicity in animal species. Bcl-2 proteins were not detectable in kidney and liver tissues by immunohistochemical staining[14] but Bcl-2 null mice developed polycystic kidneys and high serum urea nitrogen and creatinine levels. [19]Bcl-2 is probably involved in kidney development and it is not expressed or functional in fully developed kidneys. Liver developed normally in Bcl-2 null mice.[20]

[13]Silva M, et al. Erythropoietin can promote erythroid progenitor survival by repressing apoptosis through Bcl-XL and Bcl-2. Blood 1996; 88: 1576-1582.

[14] Hockenbery DM et al. BCL2 protein is topographically restricted in tissues characterized by apoptotic cell death. Proceedings of the National Academy of Science 1991; 88: 6961-6965

[15] Hafid-Medheb K, et al. Bcl-XL is required for heme synthesis during the chemical induction of erythroid differentiation of murine erythroleukemia cells independently of its antipoptotic function. Blood 2003; 101: 2575 2583.

[16] Mak SS, *et al*. Indispensable role of Bcl-2 in the development of the melanocyte stem cell. *Developmental Biology* 2006; 291: 144–153

Veis DJ, *et al*. Bcl-2-deficient mice demonstrate fulminant lymphoid apoptosis, polycystic kidneys, and hypopigmented hair. *Cell* 1993; 75: 229-240

[17] Ramiro-Ibáñez F et al. Gastric and pancreatic lesions in rats treated with a pan-CDK inhibitor. Toxicologic Pathology 2005; 33: 784–791

[18] Terrano DT, et al. Cyclin-Dependent Kinase 1-mediated Bcl-xL/Bcl-2 phosphorylation acts as a functional link coupling mitotic arrest and apoptosis. *Mol Cell Biol* 2010; 30: 640–656

[19] Veis DJ, et al. Bcl-2-deficient mice demonstrate fulminant lymphoid apoptosis, polycystic kidneys, and hypopigmented hair. Cell 1993; 75: 229-240

[20] Nakayama K et al. Targeted disruption of Bcl-2αβ in mice: Occurrence of gray hair, polycystic kidney disease, and lymphocytopenia. Proceedings of the National Academy of Science 1994; 91: 3700-3704.

In summary, the major target organs and adverse effects of venetoclax were primarily related to its pharmacological action. The most significant toxicological concern was the severe effects on male germ cell development. Haematological effects were expected, with the severity of off-target effects (on erythrocytes) generally mild and reversible. The decreased pigment in the hair follicle bulbs are likely to be clinically relevant but do not represent a major safety concern. The potential sequelae of single cell necrosis in epithelial tissues are unknown but the minimal severity in the long-term dog studies suggests this may not be a progressive lesion.

Genotoxicity

Venetoclax did not exhibit genotoxic potential in any of the GLP compliant studies. Test systems used were in vitro (Ames bacterial reverse mutation assay and chromosomal aberration assay in human peripheral blood lymphocytes) and in vivo assays (mouse micronucleus test, Comet assay). Study designs were consistent with ICH guidances[3,2] and venetoclax was appropriately tested to its limits of solubility and toxicity.

Carcinogenicity

Carcinogenicity studies on venetoclax were not conducted. ICH guidance[21] specifies that such studies are not usually required for products intended for advanced cancer indications. Nevertheless, in the Nonclinical Overview the sponsor indicated that such studies are being considered, should use be extended to include indications other than advanced cancer. In the interim, the negative findings from genotoxicity testing did not identify venetoclax as potential mutagen or clastogen and thus carcinogenic risk related to DNA damage is considered low. Furthermore, there were no signals for neoplasia noted in any of the pivotal toxicity studies at exposure durations of up to 9 months.

Reproductive toxicity

Reproductive toxicity studies were conducted in mice and rabbits in GLP compliant studies which encompassed most stages of development (fertility and embryofetal development). Pre/postnatal development was not assessed which is acceptable under ICH S9[2]. Study designs were generally satisfactory with regard to group sizes, dose selection and timing/duration of treatment. Separate fertility studies were conducted in male and female mice in which treated male and female animals were paired up with untreated female and male mice, respectively. Dosing used in the embryofetal development studies attained plasma exposures (relative to clinical AUC) that were sub-clinical at the No observable adverse effect levels (NOAELs) for both species. Fertility studies did not include toxicokinetic measurements but the same doses were used in a 4 week toxicity study and toxicokinetic parameters ascertained in this study were used to determine exposure ratios for fertility.

Relative exposure

Table 3: Relative exposure in embryofetal development studies based on plasma venetoclax (AUC_{0-24h})

Species	Study type Study no.	Dose mg/kg/day	AUC0–24 h µg·h/mL	Exposure ratio#
Mouse (Crl:CD1(ICR))	Male fertility **[R&D/12/810]**	50	21	0.6
		200	71	2.2

[21] Guideline On The Need For Carcinogenicity Studies Of Pharmaceuticals S1a

Species	Study type Study no.	Dose mg/kg/day	AUC0–24 h µg·h/mL	Exposure ratio#
Fertility#		600	86	2.6
	Female fertility **[R&D/13/279]**	50	14	0.4
		200	48	1.5
		600	98	3
Mouse (Crl:CD1(ICR)) Embryofetal development	Dose range finding study **[R&D/12/551]**	50	21.6	0.7
		300	43	1.3
		600	71.8	2.2
	Main study **[R&D/12/746]**	10	5.85	0.2
		50	26.1	0.8
		150	37.8	1.2
Rabbit (NZW) Embryofetal development	Dose range finding study **[R&D/12/543]**	50	0.72	0.02
		100	1.85	0.06
		300	4.23	0.13
	Main study **[R&D/12/824]**	50	1.38	0.04
		100	2.37	0.07
		300	4.9	0.15
Human (CLL/SLL & NHL patients)	Steady state **[M12-175]**	400 mg/day	32.8	–

= animal: human plasma AUC_{0-24h}; #data are from Study No. R&D/10/342, day 2

Venetoclax did not readily cross the placenta in mice and rabbits. While there were discernible levels of venetoclax in fetuses, these were at least 12 times lower than maternal plasma levels. Milk transfer of venetoclax was not determined in either of the tested species. Toxicokinetic measurements at the selected doses indicated that exposures attained in these studies were generally subclinical (at or less than clinical plasma AUC levels).

Fertility effects of venetoclax were assessed in treated male and female mice mated with untreated animals (50, 200 and 600 mg/kg/day, PO for 14 to 15 days prior to mating). There were no treatment-related mortalities and clinical signs were generally sporadic (high dose males: hunched posture, swollen preputial area and tachypnoea). Mating and fertility indices of the two studies did not indicate treatment-related effects. However, neither study included extensive histological examination of reproductive tissue and sperm analyses were not conducted in males. Adverse histological findings in testes and impairments to spermatogenesis were noted in the dog in the pivotal 9 month repeat dose study (see Repeat Dose Toxicity Section above). Development of these adverse effects have a pharmacological basis[22] and were seen at subclinical exposures (≥ 0.5 fold clinical AUC). In the mouse fertility studies, post-mortem assessments only took into account treatment-related effects on organ weights (seminal vesicles, testes, prostate, and epididymides). Sperm parameters and histopathology of these organs were not assessed. Nevertheless, histological lesions were not detected in reproductive organs in the repeat dose toxicity studies in mice or rats and treatment of mice with venetoclax for two weeks did not affect fertility indices, with both sexes exhibiting comparable conception rates to vehicle control groups. Slightly lower fertility indices were noted in male and female mid dose (MD) groups (88% compared to 96% for controls) but as this observation was not dose-dependent it was not considered toxicologically significant. Litter parameters

[22] Oldereid NB, et al. Expression of Bcl-2 family proteins and spontaneous apoptosis in normal human testis. Mol Hum Reprod. 2001; 7: 403-8.

(implantations or fetal viability) were also not affected by venetoclax treatment and in the female study there were no treatment-related changes of any kind. The NOAEL/No observable effect levels (NOELs) for both studies were the highest tested dose (600 mg/kg/day, PO). However, adverse effects noted in the dog studies are considered compelling enough to consider male reproductive system toxicity as a clinically relevant finding, especially since effects were not reversible.

In mouse embryofetal development studies venetoclax did not cause any maternal mortalities. A non GLP, dose-range finding study used venetoclax doses of 50, 300 and 600 mg/kg which resulted in reductions in maternal body weight gain and embryofetal losses (resorptions and post-implantation losses). Thus, doses were reduced to 10, 50 and 150 mg/kg in the GLP main study. In the main study, lower body weight gain in the high dose group (compared to control group) was associated with increased resorptions and post-implantation losses. There were no other indications of maternal toxicity. Litter parameters were affected in both preliminary and main studies, with treatment related increases in resorptions and post-implantation losses at doses ≥ 150 mg/kg (1.2 times the clinical AUC). Placental transfer was low but there was a discernible dose-related presence of venetoclax in fetuses. Adverse developmental findings (malformations and variations) were not reported in either study but there were significant treatment-related reductions in fetal body weights at ≥ 150 mg/kg in both studies. The maternal NOAEL was 150 mg/kg (1.2 times the clinical AUC), while the embryofetal development NOAEL was considered to be 50 mg/kg (0.8 times the clinical AUC).

In rabbits, a preliminary non GLP, embryofetal development study tested doses of up to 600 mg/kg/day (considered as the maximum feasible dose based on physicochemical constraints). There were no maternal mortalities and with the exception of decreased body weight gain at all doses and minor clinical observations (reduced grooming and abnormal faecal output), venetoclax appeared to be tolerated well at doses ≤ 300 mg/kg/day.

Doses selected for the main GLP study were 50, 100 and 300 mg/kg/day. Four dams from the high dose group were found dead or were euthanised between gestational day (GD) 16 and GD 25. The deaths were considered treatment related and were characterised by decreased motor activity, dehydration, thickening of the pyloric region of stomach/duodenum and abnormal faecal output. In one dam dark red colouring of the caecal serosa was noted, as well as blackening of the fundus and cardia of the stomach while in another dam the stomach and intestines were distended with gas, overall suggesting a gastrointestinal basis for moribundity. Examination of litters found embryos viable in one dam, while in the other dams, viability was uncertain as there were a number of early and late resorptions counted among the conceptuses. In the dams that survived to scheduled termination, minor clinical signs included scant or soft faeces, dehydration and poor grooming. Decreases in body weight gain were noted at the high dose but otherwise there were no other adverse findings. Venetoclax did not affect rabbit litter parameters in either the dose range finding or main studies and there was no indication of an effect on visceral or skeletal development.

Placental transfer was low in rabbits and explains the absence of developmental effects. Resorptions noted in the unscheduled necropsies of the four high dose dams were likely secondary to maternotoxicity. However in mice the resorptions and post-implantation losses as well as decreases in fetal weights were not associated with such profoundly adverse maternal effects; thus, venetoclax is still likely to be embryotoxic. The maternal NOAEL is considered to be 100 mg/kg/day (0.07 times the clinical AUC), based on mortalities seen at higher doses while the NOAEL for embryofetal effects was the highest dose (≥ 300 mg/kg/day, or 0.15 times the clinical AUC) since no adverse fetal effects were reported.

Overall, although venetoclax did not impair fertility in mice, compelling enough findings from dog studies indicated potential toxicities to the male reproductive system in humans. There was no indication that venetoclax is teratogenic but increased resorptions and post-implantation losses in mice suggest an embryotoxic effect that may or may not be secondary to maternotoxicity.

Pregnancy classification

The sponsor proposed Pregnancy Category C[23] for venetoclax. This category applies to substances that may cause harmful effects on the fetus or neonate through a pharmacological mechanism where its effects may be reversible. In mice there were increased embryofetal losses and lower body weights of surviving fetuses at high doses but there was no evidence of a teratogenic effect. Plasma exposures attained in these studies were subclinical, suggesting that embryotoxic effects may still be clinically relevant. Placental transfer was low in animal studies and risk of fetal exposure may be low. For this reason, Category C is considered acceptable.

Immunotoxicity

Due to its proposed mechanism and cellular target, immunomodulatory effects are anticipated with venetoclax. Lymphocyte phenotypes were profiled over a six month period in a limited toxicity study in dogs given single doses of venetoclax (2, 5, 30 and 100 mg/kg PO). Venetoclax had its strongest effect on B cells which were decreased at all tested doses, while other lymphocyte subtypes exhibited treatment-related reductions only at the two higher doses. Onset of decreases were apparent from 1 h post-dose and lowest (nadir) levels were reached at 24 h. Severity and reversibility of decreases were dose-related, with lower lymphocyte counts persisting at the 6 month sampling point for higher doses. The study however only considered single dosing of venetoclax. Repeat dose toxicity studies in mice (6 months), rats (13 weeks) and dogs (9 months) also showed treatment-related decreases of lymphocytes. Dogs from all dose groups of the 9 month pivotal toxicity study showed an almost complete reduction of B cell counts (>90% by Day 274, at doses that achieved plasma exposures between 0.5 to 4.2 times the clinical AUC). T-cells types (mature, helper and cytotoxic T) were also affected by treatment. This study did not include a recovery period but other studies in mice and dogs showed only partial restoration to normal lymphocyte counts at the conclusion of a 4 week recovery period. In dogs total leukocyte count were still 33 to 65% lower than vehicle controls, while in mice lymphocytes were 21 to 26% lower than controls.

Lymphocyte depletion was also noted in lymphoid tissues (GALT, mesenteric and mandibular lymph nodes, spleen and thymus) and treatment-related alterations in weights of associated organs (spleen and thymus) were observed. Resulting leukopenia may increase susceptibility to infections. In mice several deaths seen in MD and high dose (HD) groups were attributed to inflammation or infection-related causes, while in dogs evidence of chronic/subacute inflammation in lungs and erythrophagocytosis in the mandibular lymph node of a HD animal is suggestive of infections.

Overall, pharmacologically mediated reductions in lymphocytes are an expected outcome of venetoclax treatment as they underlie its mechanism of action in CLL. B cells were the most severely affected but depletion of other leukocytes was also seen at high doses. The apparent irreversible nature of these effects, even with single dosing, indicates toxicological significance. Clinical relevance of the immunotoxic effects of venetoclax is underscored by the fact that higher rates of infections were associated with treatment and are identified as a common adverse drug reaction in the proposed Product Information.

[23] Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Phototoxicity

Distribution of venetoclax into pigmented tissue (such as the uveal tract) was low in pigmented Long-Evans rats. However, based on spectral attributes of venetoclax (peak absorbance range: 206 to 428 nm; molar extinction coefficient range: 5200 to 56000 L/mol/cm), the sponsor investigated the phototoxic potential of venetoclax in hairless mice. Under the test conditions, there was no evidence of phototoxicity arising from venetoclax treatment, predicting low phototoxic potential.

Metabolite studies

Specific studies on the disproportionate human metabolite M27 were limited to in vitro assessments of genotoxicity. M27 tested negative for genotoxicity in bacterial reverse mutation and chromosomal aberration assays. M27 is also a pharmacologically active substance, albeit with much lower affinity than parent venetoclax for Bcl-2. Aside from genotoxicity, the toxicity profile of M27 is uncertain since the metabolite was absent or present at very low levels in the test species used in toxicity studies. Further information from the sponsor to support the toxicological qualification of M27 was not available at the time of completion of the nonclinical evaluation report.

Impurities

The proposed specifications for drug substance and drug product impurities are considered adequately qualified.

Paediatric use

Venetoclax is not proposed for paediatric use. Nonetheless, the sponsor submitted two dose-range finding studies in preparation for a GLP juvenile toxicity study in the event that venetoclax is extended to a paediatric indication. The two studies consisted of preliminary assessments of toxicity parameters in pups dosed with venetoclax (3, 30, 100 and 300 mg/kg/day, PO) between postnatal Days 7 and 21 and on post-natal day (PND) 30. A NOAEL was not established based on clinical signs and effects on body weight gain. The sponsor indicated that a GLP compliant study is being planned. The sponsor is requested to submit this when the final report becomes available. In response to a TGA query, the sponsor indicated that a GLP toxicity study in juvenile CD-1 mice was nearing completion and would provide the report when available (projected for September 2016).

Nonclinical summary

- The submitted nonclinical studies were in accordance with the relevant ICH guideline for the nonclinical assessment of anticancer pharmaceuticals (ICH S9). The overall quality of the nonclinical dossier was high. All pivotal safety-related studies were GLP compliant.
- Venetoclax bound to Bcl-2 with sub-nanomolar affinity, promoted apoptosis and inhibited tumour cell growth in vitro with IC_{50} values well below expected clinical plasma concentrations. Venetoclax also inhibited Bcl-XL but with much lower efficacy (EC_{50} value 65 times higher). In vivo, venetoclax decreased lymphocyte numbers in wild type mice. Venetoclax inhibited the growth of leukaemia and lymphoma cells in xenograph models. This supports the proposed clinical indication.
- Venetoclax did not have inhibitory activity against other receptors or transporters at clinically relevant concentrations.

- Safety pharmacology studies assessed effects on the cardiovascular, respiratory, and central nervous systems. No adverse effects were seen on CNS function in mice or rats, or respiratory function in mice. No significant inhibition of hERG K+ channel tail current was observed at clinically-relevant concentrations. Venetoclax did not cause abnormal ECG results in conscious dogs and is not predicted to prolong the QT interval[24] in patients.
- In animals, venetoclax had low oral bioavailability and had relatively slow absorption. Plasma half-life was long in dogs and humans but shorter in mice and rats. Plasma protein binding was very high in all species including humans (>99.99%). Tissue distribution was limited, with low penetrations to the CNS and reproductive tissues.
- In humans, there was a disproportionate metabolite (M27) that was present at levels approximately 44% of venetoclax. M27 was either not detected or present at <1% the level of venetoclax in animal plasma. M27 was pharmacologically active, but had much lower affinity for Bcl-2 compared to venetoclax (Ki of 2.2 compared to <0.01 nM). There were no other major plasma metabolites in animals or humans. The in vitro metabolite profile was generally similar between mice, dogs and humans. Venetoclax was excreted almost exclusively in the faeces, mainly as metabolites.
- Venetoclax is mainly metabolised by CYP3A4. CYP3A4 inhibitors/inducers could alter the systemic exposure to venetoclax. Venetoclax is not expected to alter the exposure of co-administered drugs that are CYP450 substrates. Venetoclax was a substrate and inhibitor of both P glycoprotein (P-gp) and BCRP, and therefore it may increase the exposure of co-administered drugs that are substrates of these transporters and its plasma concentrations may be altered by P-gp or BCRP inhibitors or inducers.
- Repeat dose toxicity studies by the oral route were conducted in mice (up to 26 weeks), rats (up to 13 weeks) and beagle dogs (up to 9 months). Maximum exposures (AUC) were subclinical in mice, and low in rats and in the 9 month dog study. Higher exposures (17 times the clinical AUC) were achieved in shorter term dog studies. Target organs for toxicity were the testes (severe atrophy and oligospermia, RE 0.5 times), the haematology system (pharmacological reductions in lymphocytes and to a lesser extent other leukocytes at subclinical exposures; reversible reductions in haemoglobin, haematocrit and to a lesser extent red cell numbers at RE ≥ 0.2 times), lymphoid tissues (pharmacological reductions in lymphocytes at subclinical exposures), hair and skin (pigment loss at RE of ≥ 1) and epithelial tissues (reversible single cell necrosis at RE ≥ 0.5 times).
- Venetoclax was not mutagenic in the bacterial reverse mutation assay or clastogenic under in vitro (human lymphocytes) or in vivo (mouse micronucleus test and Comet assay) conditions. Carcinogenicity testing was not conducted. None of the pivotal toxicity studies (of up to 9 months) showed development of neoplastic or pre-neoplastic lesions.
- Venetoclax did not readily cross the placenta in mice and rabbits, and milk transfer was not examined. Fertility studies did not identify a treatment-related effect on male or female fertility at plasma exposures approximately3 times the clinical AUC. However, effects on male fertility are predicted based on adverse testicular findings and the occurrence of oligospermia in dogs. Venetoclax did not cause developmental abnormalities in mice and rabbits. In mice, however, there were higher implantation losses and lower fetal weight gains at doses ≥ 150 mg/kg (1.2 times the clinical AUC).

[24]The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like Torsades de pointes and a risk factor for sudden death.

- Immunomodulatory effects of venetoclax (decreased lymphocyte counts, lymphocyte depletion in lymphoid organs) are expected due to its expected mechanism of action. B cells were the most severely affected but other leukocyte types were also reduced. After single dosing, at high doses, total lymphocyte counts did not completely recover to predose levels by 6 months.
- The disproportionate human metabolite M27 tested negative for genotoxicity. In response to a Section 31 question the sponsor indicated that a 4 week GLP toxicity study of M27 in mice is underway and will be provided to the TGA once available. These data were not available at the time of completion of the nonclinical evaluation report.
- Local tolerance was not specifically examined but there were no adverse histology findings consistent with poor tolerance of oral formulation venetoclax. Studies in hairless mice predicted low potential of phototoxicity for venetoclax.
- Genotoxicity and general toxicity studies provided adequate toxicological qualification for two drug product degradants and four drug substance impurities at the proposed specifications. A number of unspecified impurities were considered potentially genotoxic, with mutagenicity assays ruling out all but one as mutagens. The sponsor indicated their intention to control the mutagenic impurity at or below TTC levels.

Nonclinical conclusions and recommendation

- The primary pharmacology studies support the proposed indication for venetoclax.
- No clinically relevant hazards were identified in the secondary or safety pharmacology studies.
- The lack of exposure to M27 in the animal studies limits the confidence which can be placed on the nonclinical data. Toxicological qualification of a metabolite is not required for indications to treat advanced cancer but can be submitted as post-market studies.
- Drugs that inhibit CYP3A4, P-glycoprotein and BCRP may increase exposure to venetoclax, and venetoclax may increase exposure to substrates of P-glycoprotein and BCRP.
- The key target organs for venetoclax were the testes, haematological and lymphoid system and hair/skin:
  - Effects on leukocytes and lymphoid tissues were pharmacological but the effects on red blood cells are off-target and may occur clinically.
  - The effects on testes are clinically relevant and likely to impair male fertility.
  - The effects on pigmentation of the hair follicle bulbs can be expected clinically but are not considered to compromise safety.
- Venetoclax was not mutagenic or clastogenic. Carcinogenicity was not tested.
- Reproductive toxicity studies did not identify harmful effects on fertility and embryofetal development. However, oligospermia and atrophy/degeneration of testes in dogs predict an adverse effect on male fertility.
- The proposed Pregnancy category C is considered appropriate.
- There are no nonclinical objections to the registration of venetoclax.
  - Amendments to the draft Product Information were recommended but these are beyond the scope of this AusPAR.

– The toxicity study report for M27 should be provided to TGA for review once completed.[25]

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

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

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

The pro-survival Bcl-2 proteins play a central role in lymphocyte and CLL biology where they regulate clonal selection and survival. Employing structure-based design to identify small molecules that bind Bcl-2-like protein 1 (BCL-xL), investigators developed navitoclax, the first-generation high-affinity inhibitor of Bcl-2 family proteins. Navitoclax enhanced the effect of death signals and killed cells in a mechanistically canonical manner. A Phase I study of navitoclax showed activity in 50% of patients with relapsed or refractory CLL but inhibition of BCL-xL, a regulator of platelet senescence, led to dose-limiting thrombocytopenia. To generate a more potent and selective Bcl-2 inhibitor, navitoclax was reverse engineered which led to the development of venetoclax, a potent inhibitor of Bcl-2 with 100 times less activity against BCL-xL. Consistent with its binding characteristics, venetoclax showed markedly less thrombocytopenia but because of potent Bcl-2 inhibition, more neutropenia compared to navitoclax.

[25] The 4 week GLP-compliant toxicity study in mice with M27 was not available at the time of completion of the nonclinical evaluation report but has since been submitted to the TGA.

Guidance

Contents of the clinical dossier

Scope of the clinical dossier

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

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

The indication being sought for this new drug application is supported primarily by interim efficacy results from one Phase II pivotal study (Study M13-982), one Phase I supportive study (Study M12-175), and 2 additional supportive studies (Studies M14-032 and M13-365):

- Study M13-982 is a Phase II, open-label, multicentre, study evaluating the efficacy of venetoclax in relapsed/refractory (R/R) or previously untreated subjects with CLL harbouring 17p deletion.
- Study M12-175 is a Phase I, first-in-human, open-label, dose-escalating, multicentre study evaluating the safety and pharmacokinetic profile of venetoclax under a QD dosing schedule in subjects with R/R CLL/SLL.
- Study M14-032 is a Phase II, open-label, nonrandomised, multicentre study evaluating the efficacy and safety of venetoclax in subjects with R/R CLL after failure of a BCR signalling pathway inhibitor (ibrutinib or idelalisib treatment).
- Study M13-365 is a Phase Ib, open-label, dose-escalating, multicentre study evaluating the safety and tolerability of venetoclax in combination with rituximab in subjects with relapsed CLL/SLL.

Safety data from the above studies in addition to the following combination (2 conducted by Genentech/Roche) and biopharmaceutical studies were included in the safety analysis (limited efficacy data are available for Studies GO28440 and GP28331 and thus, were not included in the efficacy analysis):

- Study M12-175 is a Phase I, open-label, 2-arm study to evaluate the safety and pharmacokinetic profiles, to determine the MTD and RPTD of venetoclax in subjects with R/R NHL (Arm B) and to examine the food effect in the dose escalation portion of the study.
- Study GO28440 is a Phase Ib, open-label, nonrandomised, multicentre, dose-finding and safety study of venetoclax administered in combination with bendamustine/rituximab (BR) in subjects with R/R or previously untreated CLL.
- Study GP28331 is a Phase Ib, open-label, nonrandomised, multicentre, dose-finding and safety study of venetoclax administered in combination with obinutuzumab in subjects with R/R or previously untreated CLL.

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

Good clinical practice

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

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

Pharmacokinetics

Studies providing pharmacokinetic data

The 12 clinical studies contributing to the clinical pharmacology evaluation of venetoclax are listed in Table 4 (Attachment 2). Due to the testicular toxicities observed in male dogs, all healthy volunteer studies were carried out in females of non-child bearing potential.

Evaluator's conclusions on pharmacokinetics

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

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

Following multiple-dose administration, the maximum plasma concentration of venetoclax was attained by 5 to 8 hours. The harmonic mean terminal half-life ($t_{1/2}$) ranged from 17 to 41 hours following a single oral dose of venetoclax (Study M12-175) which supported the proposed daily dosing. In subjects with CLL, venetoclax showed minimal accumulation and steady-state AUC increased proportionally over the dose range of 150 to 800 mg. Venetoclax was administered with food in all clinical studies; food increased the bioavailability of venetoclax by approximately 3 to 5 times. Venetoclax is highly bound to plasma proteins with the unbound fraction < 0.01 and it is primarily eliminated as metabolites in faeces with negligible renal elimination (< 0.1%).

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

Population pharmacokinetic analyses using data from five studies in subjects with cancer (Studies M13-982, M12-175, M14-032, M13-365 and M13-364) and three studies in

healthy subjects (Studies M14-253, M14-497 and M15-101), was able to characterise venetoclax plasma concentrations over time and identify the key intrinsic and extrinsic factors affecting venetoclax pharmacokinetics. The complete identified sources of variability in the population pharmacokinetic final model were:

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

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

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

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

For the pivotal Study M13-982, at the time of dose selection there was limited complete remission data and therefore the dose was selected based on objective response rate (ORR) alone. A repeated measures logistic regression analysis between exposure and objective response conducted at the time of dose selection 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. A population pharmacokinetic (PK)/pharmacodynamic (PD) exposure response analysis on lymphocytes and tumour size was also conducted to further refine the dose selection. The established population PK/PD models based on lymphocyte and tumour response were subsequently used to predict the ORR. Based on these simulations, 84.0% of subjects in the 200 mg regimen, 87.8% of subjects in the 400 mg regimen and 89.9% in the 600 mg regimen would achieve OR by Week 24. By Week 12, the effect plateaued due to reaching a steady state with the designated cohort dose.

In M12-175, overall response rates were similar among patients who initially received doses ranging from 400 to 1200 mg per day in the dose-escalation cohort. The selection of 400 mg per day as the dose for ongoing evaluation was informed by the balance of overall

response and safety data; the selection of this dose was subsequently supported by the safety and efficacy analyses of data from the expansion cohort after a minimum of 15 months of follow-up.

The proposed PI has an adequate summary of the PK presented in the submission.

Pharmacodynamics

Studies providing pharmacodynamic data

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

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

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

Evaluator's conclusions on pharmacodynamics

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

Dosage selection for the pivotal studies

Pivotal Study M13-982

The dose of 400 mg was selected on the basis of preliminary data in relapsed/refractory CLL/SLL subjects from the ongoing venetoclax first-in-human Study M12-175. In this study efficacy was evaluated in 56 CLL/SLL subjects across 8 dose escalation cohorts (150 mg to 1200 mg) and in 60 subjects in a 400 mg safety expansion cohort. Anti- tumour activity was observed with venetoclax monotherapy in this study population of heavily pre-treated CLL/SLL subjects with relapsed or refractory disease, including those with

high risk features (17p deletion, fludarabine-refractory, IGVH unmutated and TP53 mutation without 17 p deletion). Consistent, high response rates were observed across the dose cohorts and subpopulations. Initial responses were observed early with a median time to partial remission (PR) of 1.4 months. Deeper responses were observed with longer time on treatment; median time to complete response/complete remission with incomplete blood count recovery (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. Independent endpoint review committee (IRC) assessment of disease progression and tumour response for 57 CLL subjects treated at 400 mg at the time of the interim analysis generally confirmed the findings of the overall best response based on investigators' assessments. There were some discordance between the number of investigator-determined and IRC assessed CR/CRi.

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

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

Efficacy

Evaluator's conclusions on efficacy

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

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

ORRs of 29% to 35% after standard fludaradine-based regimens.[26] However, the durability of remissions, measured by progression-free survival and the impact of venetoclax therapy on overall survival has not been defined. The sponsor has used ORR as a surrogate endpoint for PFS and overall survival (OS). Measuring ORR has the advantage of allowing effect to be attributed to venetoclax and not the natural history of R/R CLL but is not a comprehensive measure of activity and has not been directly validated in CLL studies.

To justify the use of ORR, the sponsors have referenced Badoux 2011, however this study reported associations with complete remission (CR) and nodular partial remission (nPR), not ORR, which includes CR + complete remission with incomplete bone marrow recovery (CRi) + nPR + PR. In this study of fludarabine, cyclophosphamide and rituximab (FCR) for the treatment of R/R CLL, '*superior outcomes for time-to-event endpoints were observed for patients who achieved CR or nPR'*, with estimated median PFS for patients achieving CR 60 months compared with 38 months for patients achieving nPR (P = 0.076) and 15 months for those achieving PR (P <0 .001); and time to progression (TTP) was associated with MRD status by flow cytometry for patients achieving CR. However, there was no significant difference in OS for patients achieving CR or flow MRD–negative status and there were no differences in TTP or OS according to flow or PCR MRD status in patients whose best responses were PR or nPR.1 In Tam 20083, CR was associated with OS in FCR treated R/R CLL. Patients in CR had the most favourable TTP (median: 85 months) and survival (88% at 6 years), followed by patients in nodular partial response (PR-nod) who had a shorter TTP (median: 71 months, P =0.03) but similar survival (77% at 6 years, P =0.12). Compared with PR-nod, patients in CR except for incomplete recovery of blood counts (PR-i) had similar TTP (median: 50 months, P =0.28), but experienced shorter survival (42% at 5 years, P =0.01).

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

In the submitted proposal, evidence of efficacy was presented by the sponsor for

1. patients with TP53 aberrations and/or
2. those subjects with refractory or relapsed CLL.

It was therefore considered that the proposed indication:

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

was too broad and did not define a relapsed/refractory CLL group. Furthermore, although evidence of efficacy in R/R CLL with 17p deletion had been provided, evidence of efficacy for the treatment of all patients with CLL who had received at least one prior therapy was not satisfactorily demonstrated. For each of the provided studies for efficacy, the specifically targeted CLL groups are detailed as follows:

Pivotal Study M13-982

· Targeted to subjects harbouring the 17p deletion.

[26] Badoux, X. C., et al. (2011). "Cyclophosphamide, fludarabine, alemtuzumab, and rituximab as salvage therapy for heavily pretreated patients with chronic lymphocytic leukemia." Blood 118(8): 2085-2093.
Badoux, X. C., et al. (2011). "Fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy is highly effective treatment for relapsed patients with CLL." Blood 117(11): 3016-3024.

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

Study M12-175

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

Study M14-032

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

Study M13-365

- Subjects with relapsed CLL or SLL.

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

Study M12-175

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

Study M14-032

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

Study M13-365

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

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

Within the ORR groups in each study, it was noted that CR was infrequent. However, it was considered that in clinical practice venetoclax would be used concurrently with

chemotherapy and immunotherapy regimens. The safety, and early evidence of efficacy of venetoclax in combination with rituximab was presented in Study M13-365 and the results of a Phase III study (NCT02005471), which will compare the efficacy of venetoclax plus rituximab with bendamustine plus rituximab in patients with relapsed or resistant chronic lymphocytic leukaemia are awaited.

Safety

Studies providing safety data

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

1. *TLS*: The risk of TLS with venetoclax is a result of on-target effects and rapid reduction of tumour volume. The risk is during the first 5 weeks of treatment. A low starting dose followed by gradual dose ramp-up allowed for the tumour size to be gradually reduced and was effective in reducing the risk of TLS. TLS can be managed following standard of care guidelines.
2. *Neutropenia*: Neutropenia generally resolved with standard of care measures, few events were serious and no events led to discontinuation of venetoclax. An apparent correlation with increased rate of infection was not found.

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

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

- Pivotal Study M13-982 in subjects with R/R or previously untreated CLL harbouring the 17p deletion (N = 145, 400 mg dose).
- Key supportive Study M12-175 evaluated multiple dose levels of venetoclax in subjects with R/R CLL (Arm A) (N = 116 [67 subjects at 400 mg dose]).
- Key supportive Study M14-032 in subjects with CLL that was R/R to ibrutinib or idelalisib treatment (N = 28, 400 mg dose).

The 3 ongoing venetoclax combination therapy studies listed below provided supportive safety data,

- Study M13-365 evaluated venetoclax + rituximab in subjects with relapsed CLL (N = 49)
- Study GO28440 evaluated venetoclax + bendamustine/rituximab (BR) in subjects with R/R or previously untreated CLL (N = 19).
- Study GP28331 evaluated venetoclax + obinutuzumab in subjects with R/R or previously untreated CLL (N = 20).

Patient exposure

Data from a total of 553 subjects exposed to venetoclax treatment in the pivotal and supportive studies were evaluated for safety. This included exposure to venetoclax treatment at any venetoclax dose administered as monotherapy in CLL (N = 289),

combination therapy in CLL (N = 88), monotherapy in NHL (N = 106) and in pharmacology studies (N = 70). Of the 289 subjects with R/R CLL treated with venetoclax monotherapy at any dose, 240 subjects were in the 400 mg dose group.

The safety results from the pivotal monotherapy Study M13-982 in 17p deletion CLL subjects were largely similar to the safety results in monotherapy Study M12-175 in R/R CLL (Arm A) and in monotherapy Study M14-032 in BCRi failures. Thus, the safety evaluation of 400 mg QD venetoclax monotherapy was based on the pooled dataset of all subjects who were assigned to 400 mg venetoclax in the 3 monotherapy studies (N = 240) and includes 160 subjects with 17p deletion and 44 subjects who were BCRi failures (not mutually exclusive).

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

Postmarketing data

There are no post-marketing data as venetoclax was not marketed in any country at the time of this evaluation.

Evaluator's conclusions on safety

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

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

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

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

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

First Round Benefit-Risk Assessment

Assessment of benefits

The benefits of venetoclax in the proposed usage are:

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

Assessment of risks

The risks of venetoclax in the proposed usage are:

- TLS
- Neutropenia

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

Assessment of benefit-risk balance

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

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

First Round Recommendation Regarding Authorisation

Based on the clinical data, submitted it is recommended that the application

> *Venclexta (venetoclax) is indicated for the treatment of patients with CLL who have received at least one prior therapy; this includes patients with 17p deletion*

not be approved.

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

Based on the clinical data submitted, it is recommended that the sponsor change the indication to:

> *Venclexta is indicated for the treatment of patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion.*

Second Round Evaluation of clinical data submitted in response to questions

For details of the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second Round Benefit-Risk Assessment

Second round assessment of benefits

The benefits of venetoclax in the proposed usage are:

- In patients with R/R CLL with 17p deletion, the overall response rate with venetoclax monotherapy is 79.4%.
- In patients with R/R CLL with 17p deletion, the complete response rate with venetoclax monotherapy is 7.5%.
- In patients with R/R CLL, those without the 17p deletion chromosomal aberration appear to be as sensitive to the effects of venetoclax as subjects who have the 17p deletion.

Second round assessment of risks

The risks of venetoclax in the proposed usage are:

- TLS
- Neutropenia

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

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

Second round assessment of benefit-risk balance

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

Second round recommendation regarding authorisation

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

Venclexta is indicated for the treatment of:

- *patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) with 17p deletion, or*

- *patients with relapsed or refractory CLL for whom there are no other suitable treatment options.*

Note to Indications. These indications are approved based on overall response rates. Duration of response and improvements in overall survival, progression-free survival or health-related quality of life, have not been established.

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

V. Pharmacovigilance findings

Risk management plan

Summary

- AbbVie Pty Ltd submitted EU-RMP version 1 (October 2015; DLP 30 April 2015[27]) and ASA version 1 (January 2016) with the application to register venetoclax. An updated ASA (version 1.1, August 2016) was submitted with the sponsor's response to questions.
- The sponsor later submitted EU-RMP version 2.0 (Date October 2016 data lock point (DLP) 30 April 2015[27]) and ASA version 1.2 (October 2016).
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below:

Table 4: Summary of Safety concerns

R=routine and A=additional

		Pharmacovigilance		Risk Minimisation	
		R	A	R	A
Important identified risks	Tumour lysis syndrome	ü	–	ü*	–
	Neutropenia	ü	–	ü	–
Important potential risks	Embryofetal toxicity#	ü	–	ü	–
	Testicular toxicity**	ü	–	ü	–
	Medication Error**,#	ü	–	ü*	–
	Serious infection	ü	–	ü	–
	Richter's transformation**	ü	ü	–	–
	DDI (CYP3A inducers, CYP3A inhibitors)	ü	–	ü	–
Missing information	Carcinogenicity	ü	–	ü	–
	Safety in severe hepatic impairment	ü	ü	ü	–
	Safety in severe renal impairment	ü	–	ü	–
	Safety in long-term exposure (> 12 months)	ü	ü	ü	–

[27] Various data lock points for different studies: 30 April 2015 for Studies M13-982 and M14-032 for subjects who began dosing by 26 March 2015; 10 February 2015 for Study M12-175; 15 December 2014 for Study M13-365; and 28 November 2014 for Studies GO28440 and GP28331

* = In response to TGA recommendations the sponsor has agreed to provide a patient alert card as part of their packaging in addition to their intended 'quick start guide';
# = The sponsor has added these safety concerns in response to the first round RMP evaluation;
** = changed or added in the revised EU RMP version 2.0 (October 2016) and ASA version 1.2 (October 2016.

- Routine pharmacovigilance includes the use of a targeted follow-up questionnaire for TLS. Additional pharmacovigilance activities have also been proposed. These include:
  - Four ongoing studies to assess overall safety of venetoclax, including Richter's transformation and safety in long-term exposure (>12 months)
  - One study to evaluate the effect of severe hepatic impairment on venetoclax PK and safety
  - A prospective observational cohort study to assess long-term safety
  - A drug interactions study assessing the effects of venetoclax on the pharmacokinetics of oral contraceptives in patients with haematological malignancy
  - An in vitro study to investigate the potential of venetoclax to induce CYPs 1A2 and 2B6.
- No additional risk minimisation activities are planned. In response to the RMP evaluation, the sponsor has provided further information about their intended activities to support the safe use of venetoclax in Australia:
  - The sponsor plans to conduct general healthcare professional educational and patient on-boarding activities to support the safe use of venetoclax when it is introduced into the Australian market.
  - A Patient Alert Card (PAC) has been developed in response to recommendations from the RMP Evaluator. The PAC, in addition to the 'Quick Start Guide' will be provided to patients in the packaging of the starter pack.

Outstanding Recommendations after the second round evaluation

The sponsor had adequately addressed all the first and second round recommendations, with the exception of the outstanding issues shown below. These issues have subsequently been resolved between the sponsor, clinical Delegate and RMP evaluator as detailed below:

Recommendations 15 and 16

i. The sponsor has committed to implementing healthcare professional education and a Patient Alert Card (PAC) but has categorised these activities as 'supplemental' risk minimisation activities. The RMP evaluator does not agree that these activities form part of routine risk minimisation and categorisation as 'supplemental' is inconsistent with international guidance, which considers these types of activities 'additional' (*EMA Guideline on Good Pharmacovigilance Practices (GVP), Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators)*. Therefore, these activities should be listed as additional risk minimisation activities in the ASA.

ii. The wording on the PAC with respect to the timing of blood tests and seeking healthcare professional advice should be revised to align with the advice in the Quick Start Guide.

Sponsor's Response:

(i) The sponsor maintains the position that the proposed voluntary educational and onboarding activities are 'supplemental' to normal activity, and are not appropriate for classification as 'additional risk minimisation activities' within the ASA. The proposed activities serve to support overall management of the patient, as opposed to minimising the risk of specific safety concerns such as TLS. The sponsor notes that the Delegate's Overview, which was updated to take into consideration the Delegate's review of the sponsor's responses to the second round RMP evaluation report, considers the sponsor's position as acceptable, with no further outstanding issues raised from an RMP perspective. To ensure that every patient who commences treatment with Venclexta receives the PAC, the sponsor is proposing to incorporate the Patient Alert Card (PAC) into the monthly outer carton for the starting pack as a separate insert. By doing so, the PAC will form part of the monthly starter pack, much like the Quick Start Guide, and thus, can be considered to be a routine risk minimisation measure

(ii) The wording on the PAC has been revised to include a reminder for the patient to refer to the Quick Start Guide, as well as aligning the advice given with respect to timing of blood tests and seeking healthcare professional advice.

Post second round RMP evaluator comment:

(i) It is reiterated that a PAC would normally be considered an additional risk minimisation activity. However, as the sponsor has proposed to now include it as part of the monthly starting pack, and the Delegate has agreed to this approach, the RMP evaluator has agreed to consider it as routine risk minimisation as it is part of the packaging/labelling. The sponsor should note that any changes to the packaging/labelling must have TGA approval prior to implementation. The sponsor has provided a reasonable argument for the educational and on-boarding activities to be considered routine.

The sponsor has revised the wording of the PAC with respect to the timing of the blood tests and this now aligns with the Quick Start Guide, which is acceptable.

Recommendation 17

The sponsor should consider removing reference to 'ounces' in the Quick Start Guide for use in Australia to improve the clarity of advice in this document.

Sponsor's Response: The sponsor had requested for approval for the use of US labelled weekly wallets as alternate labelling for packed product to be supplied in Australia. Due to relatively low patient numbers in Australia and subsequently, the inability to meet minimum order quantities required by the manufacturer to manufacture and pack product specifically for Australia, the sponsor will be utilising US stock and undertaking secondary packaging steps to repack the US labelled weekly wallets into an Australian (AU) specific outer monthly carton along with an AU specific Quick-start Guide and Patient Alert Card for the Starting Pack. This was considered acceptable by the TGA, with the condition that US-specific contact details and the 'Prescribing Information' statement be over-stickered with the corresponding information from the Australian labels. Given that the US labelled weekly wallets utilise imperial units when describing required water intake, the sponsor wishes to retain reference to both metric and imperial units within the Quick Start Guide for ease of reference for the patient.

Post second round RMP Evaluator comment: The sponsor' response is acceptable as the TGA has given permission to use US stock with steps to make more Australian specific.

Other advice to the Delegate PI changes

It is recommended to the Delegate that the section on 'Risk Assessment and Prophylaxis for Tumour Lysis Syndrome' under Dosage and Administration be moved so that it precedes information on Dosage.

The Delegate is requested to consider revising the wording in the PI about dose titration and timing of blood tests. The revisions should make it clear that the next dose increment should be taken then a blood test is required at an appropriate time after administration in order to establish if the patient is still at risk of TLS and whether a dose decrease is required.

In addition, the Delegate may wish to consider if the PI recommendation to hospitalise patients at high risk of TLS for the 20 and 50 mg dose initiation is sufficient or whether it should be considered for any subsequent dose escalations.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

After consideration of the sponsor's Post second round response the wording for conditions of registration is as follows:

- Implement EU RMP (version 2.0, October 2016, data lock point 30 April 2015), with Australian Specific Annex (version 1.2, October 2016, which includes the provision of a patient alert card and quick start guide in the packaging), submitted with application PM-2015-04328-1-4, and any future updates, as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The pharmaceutical chemistry evaluation was completed to the satisfaction of the evaluator. There are no outstanding chemistry issues remaining and approval for registration was recommended.

Nonclinical

The nonclinical evaluation was completed to the satisfaction of the evaluator. There were no nonclinical objections to the registration of venetoclax.

The summary of the nonclinical evaluation documented:

No clinically relevant hazards were identified in the secondary or safety pharmacology studies.

- The lack of exposure to the metabolite M27 (which is disproportionately present in human studies) in the animal studies limits the confidence which can be placed on the nonclinical data. Toxicological qualification of a metabolite is not required for indications to treat advanced cancer. However, qualification of M27 could be considered in post- market studies.[28]
- Drugs that inhibit CYP3A4, P-glycoprotein and BCRP may increase exposure to venetoclax, and venetoclax may increase exposure to substrates of P-glycoprotein and BCRP.
- The key target organs for venetoclax were the testes, haematological and lymphoid system and hair/skin:

[28] The sponsor provided the completed study report TD16-002 (4 week GLP-compliant study In mice intended to provide toxicological qualification for M27) after the finalisation of the nonclinical evaluation report.

  - Effects on leukocytes and lymphoid tissues were pharmacological but the effects on red blood cells are off-target and may occur clinically.
  - The effects on testes are clinically relevant and likely to impair male fertility.
  - The effects on pigmentation of the hair follicle bulbs can be expected clinically but are not considered to compromise safety.
- Venetoclax was not mutagenic or clastogenic. Carcinogenicity was not tested.
- Reproductive toxicity studies did not identify harmful effects on fertility and embryofetal development. However, oligospermia and atrophy/degeneration of testes in dogs predict an adverse effect on male fertility.
- The proposed Pregnancy category C is considered appropriate.
- The toxicity study report for M27 should be provided to TGA for review once completed.[28]

Clinical

The clinical evaluator recommended approval of the submission for the two amended proposed indications presented with the sponsor's responses.

Pharmacology

Twelve clinical pharmacology studies were presented for evaluation

Absorption

A significant food effect was observed, with an increase in bioavailability of 3 to 5 fold. The PI contains advice in the Dosage and administration section for patients to take whole venetoclax tablets with a meal and water at the same time each day.

Following multiple dose administration, with food, T_{max} occurred at 5 and 8 h post- dose. Plasma terminal half-life was observed as 17 to 41 h.

Dose proportionality of AUC was observed across the dose range of 150 to 800 mg.

The Delegate notes the dose proportionality as above. However, for the initial up-titration period starting at 20 mg daily, dose proportionality has not been examined. This dosing schedule was developed to minimise events of tumour lysis syndrome.

Distribution

The population estimate for apparent volume of distribution (Vdss/F) of venetoclax ranged from 256 to 321 L in subjects with CLL/SLL and NHL.

Venetoclax is highly bound to plasma proteins with unbound fraction < 0.01.

Metabolism and Interaction with other medicines

The major metabolite identified in humans was M27; activity against Bcl-2 was approximately 58 fold lower than the parent molecule.

The parent molecule and M27 are predominately metabolised by CYP3A4 in in vitro studies.

Strong CYP3A inhibitors were shown to increase venetoclax exposure (C_{max} and AUC). The PI contains a contraindication for concomitant use of strong CYP3A inhibitors at initiation and during the dose up-titration period and that moderate CYP3A inhibitors should be avoided at initiation and during dose up-titration.

Following the initial up-titration period, the dose of venetoclax should be reduced by 2 fold and 4 fold for moderate and strong CYP3A inhibitors respectively.

A discrepancy exists between the proposed Australian PI and that approved by the FDA in regard to the effect of concomitant P-gp inhibitor administration with venetoclax. The FDA label states '*Avoid inhibitor use or reduce the Venclexta dose by at least 50%*', whereas the Australian PI does not contain this advice. The Australian PI should be amended to reflect the same advice as the FDA label.

The effect of concomitant warfarin administration was only assessed with single dose venetoclax. Concomitant exposure of venetoclax and warfarin increased the C_{max} and AUC of warfarin by 18 to 28%. Given the absence of the assessment of multiple dose administration with venetoclax on warfarin exposure, it is appropriately recommended that the international normalised ratio (INR)[29] of patients receiving warfarin be monitored closely.

Excretion

A single dose mass-balance study demonstrated approximately 21% of the parent drug is excreted unchanged in faeces and >99.9% of total radioactivity was observed.

A two compartment population PK model using data from 555 patients satisfactorily described the plasma concentration-time profile. Bodyweight, age, sex, race, subject population, mild and moderate hepatic and renal impairment and weak CYP3A inhibitors and inducers had no effect on clearance.

Efficacy

The indication being sought for this new drug application is supported primarily by interim efficacy results from one Phase II study (Study M13-982), one Phase I supportive study (Study M12-175), and 2 additional supportive studies (Studies M14-032 and M13-365).

M13-982

This was a Phase II open-label single arm study of the efficacy of venetoclax in patients with relapsed/refractory or previously untreated CLL harbouring the 17p deletion (as determined by the Vysis CLL FISH probe kit).

The primary outcomes measure was overall response rate (CR + CRi + nPR + PR) per the National Cancer Institute–sponsored Working Group (NCI-WG) guidelines as assessed by the IRC in the first 70 subjects enrolled treated in the main cohort.

An ORR of 40% was tested to reject the null hypothesis.

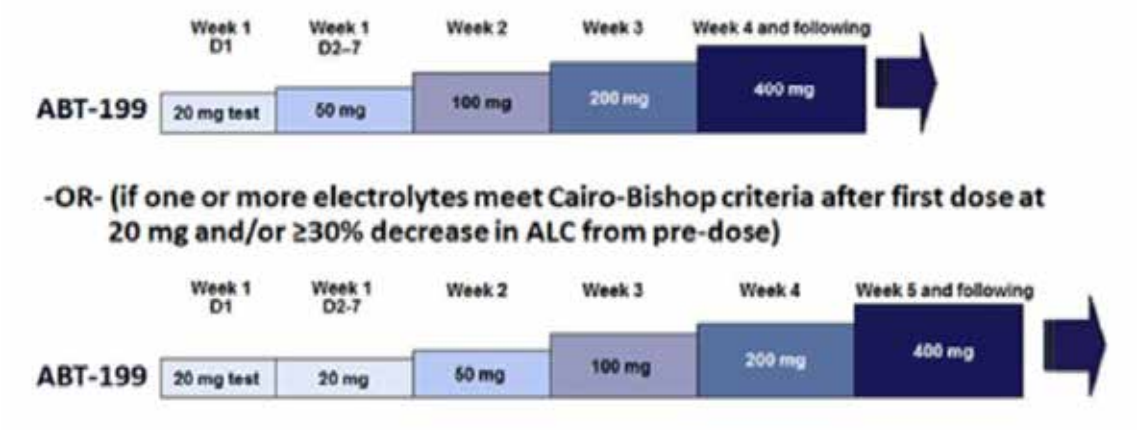
Secondary outcome measures were to:

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

The study treatment schedule was similar to that proposed for registration, excepting the dose received in the first week:

[29] INR measures the time it takes for a patient's blood to clot.

Figure 2: Study treatment schedule



A cohort of patients contributing to the safety analysis was included in this study; these patients were doses according to the up-titration schedule proposed for registration.

A total of 107 patients were enrolled in the main cohort, with 36 included in the safety expansion cohort, plus two further into the safety cohort as per a protocol amendment.

Treatment discontinuations occurred in 34.6%, with disease progression (10.3%), Richter's transformation (8.4%) and AE not related to disease progression (8.4%) being the most common reasons.

At baseline, the majority of patients (>70%) had Rai stage 0 to 2[30] or Binet stage A or B[31]; no patients had Eastern Cooperative Oncology Group (ECOG) status[32] greater than 2.

The median number of prior CLL therapies was 2 (range 1-10); 18 patients (16.8%) had received five or more lines of prior therapy.

Primary efficacy outcome

The estimate of ORR in the first 70 patients enrolled was 77.1% (95% CI 65.6, 86.3). Complete remission was observed in five patients (7.1%). Partial remission was observed in 47 patients (67.1%), with non-response in 16 (22.9%).

Independently assessed best response of overall response was demonstrated in 85/107 patients (79.4% (95% CI 70.5%, 86.6%)).

Secondary outcomes

At the time of the dossier submission, the data regarding duration of response was immature and median duration of PFS had not been reached. The proportion of patients with PFS at 12 months was 72% (95% CI 61.8, 79.8).

The estimate of median duration of OS could not be established. However, the proportion of patients alive at 12 months was 86.7% (95% CI 78.6, 91.9).

[30] The Rai staging system is one of the two staging systems currently adopted in assessment of chronic lymphocytic leukaemia (CLL). It comprises of Stages 0 to IV and classifies chronic lymphocytic leukemia into low, intermediate and high-risk categories, which correspond with Stages 0, I and II, and III and IV, respectively:

[31]The Binet staging system is one of the two staging systems currently adopted in assessment of chronic lymphocytic leukaemia (CLL). It classifies CLL according to the number of lymphoid tissues that are involved (i.e. the spleen and the lymph nodes of the neck, groin, and underarms), as well as the presence of anaemia or thrombocytopaenia.

[32] ECOG status describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability (walking, working, etc.).

EORTC QLC-C30[33] patient reported outcome measures were captured in this study. Given the single-arm nature of the study, the results are non-confirmatory of a benefit form venetoclax.

Up to treatment Week 48, there were inconsistent changes in outcomes compared to baseline across the parameters evaluated in this tool. However, the assessment of global health status was seen to improve after 4 weeks on study as compared to baseline.

Study M12-175

This was a two-arm dose escalation and safety expansion Phase I study evaluating the safety and pharmacokinetics of venetoclax in subjects with R/R CLL/SLL.

The primary outcome was to assess the safety profile, PK, maximum tolerated dose and optimal regimen of venetoclax therapy.

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

Subjects with relapsed or refractory NHL participated in Arm B of this study.

The study treatment regimen underwent multiple amendments due to the occurrence of TLS among participants. Ultimately, the dosing schedule was amended to include a 5 week up-titration period, followed by dosing at 400 mg.

Efficacy outcomes in this study were exploratory.

In total, 116 patients with CLL or SLL comprised the efficacy population, having received at least one dose of venetoclax.

Baseline patients and disease characteristics are detailed in Attachment 2.

The exploratory assessment of overall response showed a similar proportion of patients in the initial dose escalation (n=56) and safety expansion cohort (n=60) of 76.8% and 81.7% respectively.

Among patient treated with a final venetoclax dose of 400mg, independently reviewed overall response rate was 73.7% (95% CI 60.3, 84.5).

The median duration of PFS could not be estimated due to data immaturity. However, the proportion of patients who were PF at 12 months was 72.5% (95% CI 58, 83).

In their response, the sponsor presented an unsolicited efficacy update for this study in support of the proposed indication for use of venetoclax in patients without 17p deletion and no remaining treatment options.

The updated estimates of efficacy endpoints are shown below:

[33] The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients. It is supplemented by disease-specific modules for e.g. Breast, Lung, Head & Neck, Oesophageal, Ovarian, Gastric, Cervical cancer, Multiple Myeloma, Oesophago-Gastric, Prostate, Colorectal Liver Metastases, Colorectal and Brain cancer which are distributed by the EORTC Quality of Life Department.

Table 5: Investigator assessed response Study M12-175

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

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

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

Table 6: Investigator assessed duration of response and PFS in Study M12-175

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

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

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

The ORR for all subjects was consistent with that previously presented.

Among the 40 patients without 17p deletion, the non-inferential estimate of median PFS was 40 months, with approximately 65% patients experiencing PFS at 24 months.

Study M13-365

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

The primary objectives of this study were to assess the safety profile, determine the maximum tolerated dose (MTD), and establish the RPTD of venetoclax when administered in combination with rituximab in subjects with relapsed CLL or SLL.

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

The assessment of ORR in this study was per investigator. Among 49 patients eligible for an efficacy assessment, the ORR was 81.6% (95% CI 68.0, 91.2).

Neither PFS nor OS was assessed in this study population.

Study M14-032

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

The primary outcome measure was investigator assessment of response.

Among 22 patients previously exposed to ibrutinb included in the study, 15 were assessable for response. Results of partial response and stable disease were seen for 53% and 40% of patients respectively.

Among six subjects who had been previously treated with idelalisib, four were eligible for assessment of response and two had partial response; one with stable disease and one with disease progression.

Safety

Safety data was obtained from participants in the efficacy studies described above. In addition, the following studies were included in the safety analysis:

- Study M12-175 is a Phase I, open-label, 2-arm study to evaluate the safety and pharmacokinetic profiles, to determine the MTD and RPTD of venetoclax in subjects with R/R NHL (Arm B) and to examine the food effect in the dose escalation portion of the study.
- Study GO28440 is a Phase Ib, open-label, non-randomised, multicentre, dose- finding and safety study of venetoclax administered in combination with bendamustine/rituximab (BR) in subjects with R/R or previously untreated CLL.
- Study GP28331 is a Phase Ib, open-label, non-randomised, multicentre, dose- finding and safety study of venetoclax administered in combination with obinutuzumab in subjects with R/R or previously untreated CLL.

Safety was assessable for a total of 377 patients.

The numbers of participants in each trial were:

M13-982 N = 145, 400 mg dose

M12-175 N = 116 [67 subjects at 400 mg dose]

M14-032 N = 28, 400 mg dose

M13-365 N = 49 GO28440 N = 19 GP28331 N = 20

The safety population of efficacy study M13-982 comprised data from 145 patients, of which 75 (51.7%) had received venetoclax for over 48 weeks.

Exposure

The median duration of venetoclax exposure in this study was 11.2 months (range 0 to 21.5).

Discontinuations and dose reductions

Adverse events leading to study discontinuation or venetoclax discontinuation (for any reason) occurred in 59 patients (40.7%).

Adverse events leading to venetoclax interruption or dose reduction occurred in 25 patients (17.2%).

Deaths

Eleven patients among the 145 comprising the safety population died (10.3%). Four subjects had a cause of death not considered due to progression of CLL including: haemorrhagic stroke, liver derangement, septic shock and cardiorespiratory insufficiency. The investigator considered none of the adverse events leading to death to be related to venetoclax.

Adverse events

The majority of all patients comprising the safety cohort (141/145, 97.2%) experienced any adverse event with 69% experiencing a Grade ≥ 3 event. Twelve patients (11.2%) experienced a fatal adverse event

The pattern of AEs (by preferred term or system organ class) with assigned causality of 'possibly being related to study drug treatment' is shown below:

Table 7: Pattern of AEs with assigned causality of 'possibly being related to study drug treatment'

Adverse event	Total (N = 145) n (%)
Anaemia	16 (11.0)
Neutropenia	45 (31.0)
Thrombocytopenia	14 (9.7)
Diarrhoea	20 (13.8)
Nausea	30 (20.7)
Fatigue	18 (12.4)
Pyrexia	12 (8.3)
Hyperkalaemia	8 (5.5)
Hyperphosphataemia	16 (11.0)
Tumour lysis syndrome	8 (5.5)
Infections and Infestations	25 (17.2)
Musculoskeletal and Connective Tissue Disorders	9 (6.2)
Nervous System Disorders	12 (8.3)
Skin and Subcutaneous Tissue Disorders	19 (13.1)

Treatment-emergent adverse events occurring in >5% of all treated patients are shown below:

Table 8: Treatment-emergent adverse events occurring in >5% of all treated patients

MedDRA (v17.1) System Organ Class Preferred Term	Main Cohort (N = 107) n (%)	Safety Expansion Cohort (N = 38) n (%)	Total (N = 145) n (%)
Any Adverse Event	**103 (96.3)**	**38 (100)**	**141 (97.2)**
Blood and Lymphatic System Disorders	**65 (60.7)**	**17 (44.7)**	**82 (56.6)**
Anaemia	29 (27.1)	8 (21.1)	37 (25.5)
Autoimmune haemolytic anaemia	8 (7.5)	2 (5.3)	10 (6.9)
Febrile neutropenia	5 (4.7)	3 (7.9)	8 (5.5)
Neutropenia	46 (43.0)	11 (28.9)	57 (39.3)
Thrombocytopenia	20 (18.7)	5 (13.2)	25 (17.2)
Cardiac Disorders	**12 (11.2)**	**0**	**12 (8.3)**
Ear and Labyrinth Disorders	**11 (10.3)**	**1 (2.6)**	**12 (8.3)**
Vertigo	7 (6.5)	1 (2.6)	8 (5.5)
Eye Disorders	**10 (9.3)**	**1 (2.6)**	**11 (7.6)**
Gastrointestinal Disorders	**67 (62.6)**	**23 (60.5)**	**90 (62.1)**
Abdominal pain	7 (6.5)	2 (5.3)	9 (6.2)
Constipation	11 (10.3)	5 (13.2)	16 (11.0)
Diarrhoea	31 (29.0)	11 (28.9)	42 (29.0)
Nausea	31 (29.0)	12 (31.6)	43 (29.7)
Vomiting	16 (15.0)	1 (2.6)	17 (11.7)
General Disorders and Administration Site Conditions	**60 (56.1)**	**11 (28.9)**	**71 (49.0)**
Chills	8 (7.5)	0	8 (5.5)
Fatigue	23 (21.5)	5 (13.2)	28 (19.3)
Oedema peripheral	8 (7.5)	2 (5.3)	10 (6.9)
Pyrexia	21 (19.6)	2 (5.3)	23 (15.9)
Hepatobiliary Disorders	**5 (4.7)**	**0**	**5 (3.4)**
Immune System Disorders	**8 (7.5)**	**0**	**8 (5.5)**
Infections and Infestations	**77 (72.0)**	**16 (42.1)**	**93 (64.1)**
Nasopharyngitis	15 (14.0)	2 (5.3)	17 (11.7)
Pneumonia	9 (8.4)	1 (2.6)	10 (6.9)
Respiratory tract infection	9 (8.4)	0	9 (6.2)
Upper respiratory tract infection	16 (15.0)	4 (10.5)	20 (13.8)
Urinary tract infection	10 (9.3)	1 (2.6)	11 (7.6)
Injury, Poisoning and Procedural Complications	**14 (13.1)**	**3 (7.9)**	**17 (11.7)**
Investigations	**39 (36.4)**	**6 (15.8)**	**45 (31.0)**
Blood creatinine increased	7 (6.5)	2 (5.3)	9 (6.2)

Table 8 continued: Treatment-emergent adverse events occurring in >5% of all treated patients

Metabolism and Nutrition Disorders	**51 (47.7)**	**12 (31.6)**	**63 (43.4)**
Hyperkalaemia	5 (4.7)	6 (15.8)	11 (7.6)
Hyperphosphataemia	17 (15.9)	3 (7.9)	20 (13.8)
Hypokalaemia	11 (10.3)	2 (5.3)	13 (9.0)
Tumour lysis syndrome	5 (4.7)	3 (7.9)	8 (5.5)
Musculoskeletal and Connective Tissue Disorders	**32 (29.9)**	**11 (28.9)**	**43 (29.7)**
Arthralgia	6 (5.6)	2 (5.3)	8 (5.5)
Back pain	11 (10.3)	3 (7.9)	14 (9.7)
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	**24 (22.4)**	**0**	**24 (16.6)**
Malignant neoplasm progression	11 (10.3)	0	11 (10.3)
Nervous System Disorders	**34 (31.8)**	**13 (34.2)**	**47 (32.4)**
Dizziness	5 (4.7)	4 (10.5)	9 (6.2)
Headache	12 (11.2)	6 (15.8)	18 (12.4)
Psychiatric Disorders	**11 (10.3)**	**4 (10.5)**	**15 (10.3)**
Renal and Urinary Disorders	**7 (6.5)**	**0**	**7 (4.8)**
Reproductive System and Breast Disorders	**2 (1.9)**	**0**	**2 (1.4)**
Respiratory, Thoracic and Mediastinal Disorders	**30 (28.0)**	**6 (15.8)**	**36 (24.8)**
Cough	10 (9.3)	1 (2.6)	11 (7.6)
Skin and Subcutaneous Tissue Disorders	**28 (26.2)**	**7 (18.4)**	**35 (24.1)**
Rash	7 (6.5)	3 (7.9)	10 (6.9)
Vascular Disorders	**16 (15.0)**	**1 (2.6)**	**17 (11.7)**

Treatment-emergent Grade 3 or 4 AEs (by preferred term or SOC) are shown below:

Table 9: Treatment-emergent Grade 3 or 4 AEs

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

Adverse event	Total (N = 145) n (%)
Respiratory, Thoracic and Mediastinal	4 (2.8)
Vascular Disorders	7 (4.8)
Hypertension	4 (2.8)

As a result of the design of the studies comprising those evaluated for safety, the comparative risks of treatment with venetoclax cannot be established from the data provided.

Adverse events of special interest

Tumour lysis syndrome

The occurrence of TLS was identified in the clinical development program, leading to modifications to the up-titration dosing schedule. Recommendations for patient management based upon an individual assessment of tumour burden and risk are contained in the product information.

Haematological

Non-immune and auto-immune cytopaenias affecting red and white cell line as well as platelets were observed among the safety population.

Lymphopaenia and atypical infections

Lymphopaenia occurred in 11/240 patients who received 400mg daily.

Two patients with 17p deletion were identified as having pneumocystis jirovecii pneumonia; both had received venetoclax 400 mg.

No patients were reported to have infection with John Cunningham (JC) virus or develop progressive multifocal leucoencephalopathy.

One death in Study M13-982 in a man due to a treatment-emergent adverse event was associated with neutropaenia and pneumocystis pneumonia, cytomegalovirus and herpes zoster.

Leukostasis

No events of leukostasis were reported in the Summary of safety.

Bleeding

Concomitant treatment with anti-coagulants was reported for 42% of the 240 patients who received venetoclax 400mg daily. The incidence of haemorrhage among this group was 13.8% (n=33). Grades 3 or 4 haemorrhage occurred in 9 patients.

Hepatobiliary disorders

Of ten events occurring in this system organ class (SOC) among the 240 patients who received venetoclax 400 mg daily, one fatal SAE was reported but was not assessed as treatment-related.

One event of drug-induced liver injury was reported from Study GO27878 and was assigned as related to venetoclax, obinutuzumab, cyclophosphamide, doxorubicin, vincristine and prednisone.

Cardiac

Atrial fibrillation and flutter occurred in 9 (3.8%) & 1 (0.4%) of patients receiving 400 mg daily respectively. Five events of atrial fibrillation were Grade ≥ 3.

No events of Torsade de pointes were reported.

Non-significant increases in QT interval were observed.

Gastrointestinal

The incidence of diarrhoea among patients receiving venetoclax 400 mg daily was 35.4% (85/240); Grade 3 events occurred in 2 patients. No Grade 4 events were reported.

Nausea and vomiting occurred in 33.3% and 14.6% of patients in the 400 mg analysis set respectively.

There were no reported cases of intestinal perforation among the participants in Study M13-982 however this remains a risk for any patient with intestinal CLL deposits.

Second malignancies

Patients with CLL are known to be at risk of developing second malignancies. The sponsor has stated that '*a causal association of venetoclax to second primary malignancy has not been established and thus, is no longer assessed as an identified or potential risk for venetoclax*'.

Among patients receiving venetoclax 400 mg daily, the incidence of second malignancy was 11.7% (28/240). The commonest events were non-melanoma skin cancers, without an apparent preponderance of any form of other malignancies.

Risk management plan

Additional risk minimisation activities have been accepted as required by the sponsor. A patient safety card addressing the identified and potential risks, in particular TLS is to be implemented.

The sponsor is to implement healthcare professional education activities, including an 'on-boarding' program.

A patient alert card and 'quick start guide' are to be implemented.

Risk-benefit analysis

Delegate's considerations

Efficacy

The efficacy studies presented represent a package designed for conditional registration pathways.

Between studies a relatively stable estimate of overall response rate was observed, among patients with and without 17p deletion. The primary outcome measure of overall response rate has been previously sufficient for product registration. In the current application, ORR is considered appropriate for venetoclax registration for use in patients with relapsed or refractory CLL with 17p deletion and for patients with relapsed or refractory CLL without 17p deletion and no other treatment option.

The efficacy studies do not contain consistently mature data pertaining to OS or PFS among patients with and without 17p deletion. Furthermore, given the lack of randomised studies, the patient reported outcome measures presented are supportive for registration but do not represent confirmed benefit. This poses a challenge for prescribers to be able to satisfactorily obtain informed consent. As such, the product information for venetoclax must contain the 'Note to the indication' which documents the outcomes upon which registration is made. The unsolicited efficacy update for Study M12-175 does not permit

removal of reference to PFS in the note to the indication as this is an investigator-assessed secondary outcome in a single-arm study and no accompanying safety data was presented.

The incidence of Richter transformation among Study M13-982 participants of 8.4% cannot be directly compared to other cohorts of CLL patients. However, the overall risk has been reported as up to 15%.[34]

Safety

The total safety population presented comprised data pertaining to 377 recipients of venetoclax. The clinical development program to date has identified a number of important adverse events, however, given the relatively small number of patients exposed and lack of randomised trial evidence as well as a lack of exposure-adjusted adverse event rate reporting, the absolute incidence of uncommon events (by definition occurring in > 1000 patients) or those even rarer cannot be established. Furthermore, rarer yet significant events, such as progressive multifocal leucoencephalopathy, herpes simplex or hepatitis B reactivation, which have all been observed with CLL therapies but may not yet have been reported as insufficient patients have been exposed and require ongoing pharmacovigilance. It is a condition of registration (see below) that additional safety studies are presented for evaluation by the TGA.

In the absence of comparative data from a randomised controlled trial, the sponsor's assertion that venetoclax is not associated with second primary malignancies is premature. For the randomised controlled trial described in the conditions of registration below, the sponsor is required to provide a considered analysis of the risk of second primary malignancy, including adjustment for venetoclax exposure.

The risk of Richter transformation seen in the venetoclax clinical development program to date cannot be directly compared to the historical estimate of risk reported.

It is recognised that CLL therapies are associated with, or causal for, atypical infections or re-activation of prior viral infections. The sponsor has not provided sufficient discussion as to the use of prophylaxis against atypical infection or recommendations for vaccination prior to commencing venetoclax. This should be addressed in the sponsor's response and provide appropriate advice in the draft PI.

RMP

The RMP evaluator sought the advice of the Delegate on the following items:

1. It is recommended to the Delegate that the section on 'Risk Assessment and Prophylaxis for Tumour Lysis Syndrome' under Dosage and Administration be moved so that it precedes information on Dosage.

Delegate response: The Delegate considers the current position in the PI of the section on 'Risk assessment and prophylaxis for tumour lysis syndrome' to be appropriate.

2. The Delegate is requested to consider revising the wording in the PI about dose titration and timing of blood tests. The revisions should make it clear that the next dose increment should be taken then a blood test is required at an appropriate time after administration in order to establish if the patient is still at risk of TLS and whether a dose decrease is required.

Delegate comment: The decision to increase the dose to the next increment is not solely based upon the results of the patient blood tests but also the clinical history and

[34]Chigrinova, E et al. Two main genetic pathways lead to the transformation of chronic lymphocytic leukemia to Richter syndrome. Blood 2013; 122:2673-2682

examination of the patient. Since patients will be managed by experienced clinicians, this proposed change is superfluous.

3. In addition, the Delegate may wish to consider if the PI recommendation to hospitalise patients at high risk of TLS for the 20 and 50 mg dose initiation is sufficient, or whether it should be considered for any subsequent dose escalations.

Delegate comment: The assessment of a patient's risk of developing TLS is a clinical decision, not solely based upon the week of the up-titration phase. In this instance, it is not the role of the TGA to mandate where patients are, or are not, managed.

Sponsor's response to the second round RMP evaluation report was provided 28 October 2016.

The Delegate considers that the responses of the sponsor are satisfactory, with no remaining issues outstanding.

Dose

The proposed up-titration dosing schedule is designed to reduce the risk of tumour lysis syndrome occurring.

Given that venetoclax will only be prescribed by clinicians experienced in CLL management, it is considered acceptable that the dose titration pack for the four weeks of treatment may be given to the patient. As per the PI, the patient should present for repeat blood count and clinical assessment at the beginning of each dose change during this period.

Indication

The sponsor's use of the term 'available treatment option' has an implication for not only TGA registered products but also those with funded access. Patients may still access therapies not registered by the TGA or funded through Pharmaceutical Benefits Advisory Committee (PBAC) via special access. A preferred term would be 'suitable treatment option'.

The Delegate considers the appropriate wording of the indications and associated 'note to the indication' to be:

> *Venclexta is indicated for the treatment of relapsed or refractory chronic lymphocytic leukaemia (CLL) with 17p deletion.*
>
> *Venclexta is indicated for the treatment of patients with relapsed or refractory CLL without the 17p deletion for whom there are no suitable treatment options.*
>
> *Note to indication. These indications are approved based on overall response rates. Duration of response and improvements in overall survival or health-related quality of life have not been established.*

The wording of the 'Note to the indication' documents the nature of the data upon which the decision for registration has been made and must be presented in full in all venetoclax marketing materials produced by the sponsor until such time as it is amended or removed completely.

Deficiencies of the data

Across the studies presented for evaluation, the data is non-randomised and immature, precluding the demonstration of a confirmed benefit from venetoclax in terms of OS and PFS.

The requirement of the FDA for the sponsor to provide a confirmatory Phase III efficacy study as per the registration under accelerated approval underlines the provisional nature of the data presented to the TGA.

The absence of a formal study in patients with hepatic impairment is to be addressed by the sponsor.

Conditions of registration

1. The wording of the RMP condition for registration recommended by the RMP evaluator is:

   The EU-RMP (version 1.0, October 2015, data lock point 30 April 2015), with Australian Specific Annex (version 1.1, August 2016), submitted with application PM-2015-04328-1- 4, to be revised to the satisfaction of the TGA, must be implemented.

2. The sponsor is required to present the results of the three studies described in the accelerated approval decision letter of the FDA to the TGA for evaluation as Category 1 submissions:

   - PMR # 3068-1: Submit the complete final report and data from ongoing trial GO28667, a randomized, Phase 3 trial comparing VENCLEXTA (venetoclax) and rituximab with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia (CLL), including CLL with deletion 17p.
   - PMR # 3068-2: Evaluate the effect of hepatic impairment on the pharmacokinetics and safety of VENCLEXTA (venetoclax) compared to subjects with normal hepatic function. Submit a complete final report with all supporting datasets for trial M15-342 entitled, 'A Study to Evaluate the Safety and Pharmacokinetics of a Single Dose of Venetoclax in Female Subjects with Mild, Moderate, or Severe Hepatic Impairment.
   - PMR # 3068-3: Evaluate the effect of VENCLEXTA (venetoclax) co-administration on pharmacokinetics of a probe substrate of P-gp. Submit a complete final trial report with all supporting datasets.

Summary of Issues

A satisfactory assessment of safety and efficacy was possible for patients with CLL and 17 p deletion.

A satisfactory assessment of efficacy was possible for patients with CLL without 17p deletion, with no other treatment options. However, a separate safety profile for these patients was not presented.

The pivotal, non-randomised, study relies upon overall response rate as the primary outcome measure and the proposed documentation in the PI reflects this level of evidence.

Data from all non-randomised studies pertaining to OS and PFS are not yet mature.

The safety data presented for venetoclax cannot yet satisfactorily demonstrate the comparative profile against other registered products. The results of an ongoing Phase III randomised controlled trial are awaited.

Owing to the un-randomised and early data, a note to the indication, clinical trials statement and patient safety card are proposed to enable clinicians to safely prescribe venetoclax.

Proposed action

The Delegate had no reason to say, at this time, that the application for venetoclax should not be approved for the following modified indications:

> *Venclexta is indicated for the treatment of relapsed or refractory chronic lymphocytic leukaemia (CLL) with 17p deletion.*
>
> *Venclexta is indicated for the treatment of patients with relapsed or refractory CLL without the 17p deletion for whom there are no suitable treatment options.*
>
> *Note to indication. The indication is approved based on overall response rates. Duration of response and improvements in overall survival or health-related quality of life have not been established.*

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. *What is the opinion of the Committee regarding the population(s) in whom the efficacy and safety of venetoclax have been satisfactorily demonstrated to permit registration?*
2. *Given the un-randomised nature of the safety data, does the committee consider a black box warning necessary to warn for events of atypical infection?*
3. *Does the Committee consider there should be any additional measures to enable prescribers to obtain informed consent and inform patients of potential risks of venetoclax therapy?*

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

The sponsor here responds to the Delegate's request for ACPM advice on the following issues:

1. ***What is the opinion of the committee regarding the population(s) in whom the efficacy and safety of venetoclax have been satisfactorily demonstrated to permit registration?***

Sponsor's response

The sponsor maintains that the clinical data submitted for evaluation demonstrate a favourable benefit/risk ratio for the indication being sought, and thus support registration.

Clinical efficacy has been demonstrated in R/R CLL patients harbouring 17p deletion as well as in the R/R population who have no other suitable treatment options available.

The clinical data provided for evaluation consist of one pivotal Phase II single arm study in R/R CLL subjects harbouring 17p deletion (M13-982), supported by one Phase I single arm, dose-escalation study (M12-175), which includes R/R CLL and SLL subjects. Two additional supportive studies were provided: Study M14-032, a Phase II, two-arm study, which provided evidence of venetoclax monotherapy activity in CLL subjects who were refractory to ibrutinib or idelalisib; and Study M13-365, a Phase Ib one-arm study of the safety and tolerability of venetoclax in combination with rituximab in subjects with relapsed CLL/SLL. ORR's of between 73% (M12-175) and 79% (M13-982) across molecular prognostic groups and 12 month progression-free survival (PFS) estimated at 72% demonstrated that venetoclax monotherapy is effective in R/R CLL. The data have also shown that venetoclax is safe when combined with rituximab (M13-365). Moreover,

in patients with R/R CLL and abnormalities of chromosome 17p, ORR with venetoclax was significantly improved (79%) compared to previous ORRs of 29% to 35% after standard fludaradine-based regimens.

Review of the safety data from submitted studies support a favourable profile, which has been measured by the frequency and severity of AEs, SAEs, AEs leading to discontinuation, and select AE's. Venetoclax safety results were consistent across multiple trials, which serve to underline the reliability of the risk assessment.

Evaluation of overall clinical safety of venetoclax for the treatment of CLL included a total of 553 subjects who received at least 1 dose of venetoclax. In the monotherapy studies, the most commonly reported related AEs were neutropenia (25%to- 41%) and nausea (20% - 47%). The 3 most common Grade 3 or 4 adverse events were neutropenia (25% to 41%), anaemia (12% to 28%), and thrombocytopenia (12% to 18%). Adverse events reported in combination therapy studies (ongoing) were similar to those reported in the monotherapy studies.

Two important risks were identified when treating R/R CLL with venetoclax: TLS), and neutropenia. Both are considered by the sponsor and the Clinical evaluator to be consistent with a Bcl-2 mechanised base toxicity in the CLL setting. TLS is a recognised risk within the haematology setting, and can be managed following standard of care guidelines. The risk is as a result of the on-target effects and rapid reduction of tumour volume with venetoclax, which is primarily limited to the first 5 weeks of treatment. To address this risk, the sponsor implemented a low starting dose followed by gradual dose ramp-up thus allowing for gradual reduction of the tumour size. This dose ramp-up schedule is reflected in the PI, Consumer Medicine Information (CMI) and enhanced packaging as well as current Phase II and III trials. Based on experience in clinical trials, these routine risk minimisation measures have been shown to be effective in reducing the risk of TLS. In addition, prophylactic measures including adequate hydration and laboratory monitoring of blood chemistries have been included in the proposed PI, CMI and packaging, as well as added to study protocols for ongoing trials.

Neutropenia, when reported during clinical trials, were generally resolved with standard of care measures. Few events were identified as serious, and no events led to discontinuation of venetoclax. No apparent correlation with increased risk of infection was found.

In addition to the 17p deletion R/R CLL population, the sponsor believes that there remains an unmet medical need in a subset of R/R CLL patients for whom there are no other available treatment options. The sponsor believes that venetoclax has the ability to meet this need, through its unique mechanism of action and favourable safety profile, especially in patients who have been treated with prior therapies and have either demonstrated limited disease control (represented by low response rates and limited progression free survival), developed significant toxicities such as increased risk of serious infections, or both. In the sponsor's response to questions, longer-term follow-up data from key Study M12-175 was provided to further support a positive benefit/risk assessment in R/R CLL patients, particularly when comparing 17p deletion versus non 17 deletion patients. The updated study data demonstrated response is obtained in all R/R CLL patients; investigator assessed ORR was similar for those with or without 17p deletion (75.0% versus 80.0%, respectively), with median PFS being 15.6 months for those with 17p deletion, and 41.4 months for those without 17p deletion. The response is durable in patients with 17p deletion and in patients without the mutation. The non 17p-del R/R CLL patients being represented by the proposed indication have very limited treatment options. Venetoclax has shown to be effective in this population. Collectively, the efficacy data, along with the favourable tolerability/safety profile, shows that venetoclax offers an alternative therapy for those patients who have no other suitable therapeutic options available. Based on the data presented and the unique mechanism of

action of venetoclax, including its safety profile, the sponsor submits that there are sufficient data to conduct a robust risk benefit analysis, and find that there is sufficient evidence to support registration for Venclexta in the treatment of patients with relapsed or refractory CLL with 17p deletion as well as patients with R/R CLL without the 17p deletion for whom there are no suitable treatment options.

2. ***Given the un-randomised nature of the safety data, does the committee consider a black box warning necessary to warn for events of atypical infection?***

Sponsor's response

The sponsor has considered atypical infections to refer to opportunistic infections. In the submission, there were only 7 opportunistic events identified in the 400 mg dataset (240 patients). Only in 3 subjects were the events serious and all resolved with standard medical care and venetoclax dose interruptions. There were no dose reductions or discontinuations due to events of opportunistic infections. No trend for opportunistic infections was observed with venetoclax. The observed events are consistent with what is expected in subjects with refractory/relapsed CLL who have been heavily pre-treated with multiple cytotoxic agents. The sponsor does not consider a black box warning necessary to warn for events of atypical infection.

- For consideration by the ACPM, a Physician's letter which specifically relates to the Delegate's query regarding atypical infection has been provided.

3. ***Does the Committee consider there should be any additional measures to enable prescribers to obtain informed consent and inform patients of potential risks of venetoclax therapy?***

Sponsor's response

The sponsor believes that routine risk minimisation measures which include the PI for physicians and other treating healthcare professionals, the CMI and enhanced package with a 'Quick Start Guide' for patients, along with the patient alert card, both of which are proposed to be contained within the monthly carton, are sufficient to inform patients of potential risks of venetoclax therapy and ensure safe use of Venclexta.

The PI and CMI provide detailed information that the sponsor considers key to minimising the risk of TLS, the 5 week dose ramp-up period, assessment and stratification of patients at risk of TLS predicated on baseline risk factors, prophylactic measures to minimise risk of TLS and laboratory monitoring (pre and post dose) to mitigate the occurrence or severity of TLS. In addition to the PI and CMI, patients will receive enhanced packaging with a Quick Start Guide which has been validated to prevent medication errors, provide hydration messages and includes a reminder for laboratory monitoring.

The patient alert card will inform patients of key risks, in particular TLS, which may occur with venetoclax use and also provides guidance on prophylactic measures that should be taken to minimise risk. The patient alert card is also proposed to be included in the monthly carton.

Delegate's Overview Safety

It is recognised that CLL therapies are associated with, or causal for, atypical infections or re-activation of prior viral infections. The sponsor has not provided sufficient discussion as to the use of prophylaxis against atypical infection or recommendations for vaccination prior to commencing venetoclax. This should be addressed in their response and provide appropriate advice in the draft PI.

Sponsor's response

Infection is a potential risk secondary to neutropenia (an identified risk for venetoclax) or background CLL disease and R/R disease. With respect to immunisation, there are no data on use of venetoclax with immunisation. The US PI provides the following advice: '*Do not administer live attenuated vaccines prior to, during, or after treatment with Venclexta until B-cell recovery occurs*'. The proposed Australian PI has been drafted to reflect the same. The duration of the period of time appropriate prior to initiation of venetoclax therapy is considered to be best left to the clinician's judgement.

Advisory Committee Considerations

The ACPM resolved to recommend to the TGA Delegate of the Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Venclexta tablet containing 10 mg, 50 mg and 100 mg of venetoclax to have an overall positive benefit–risk profile for the amended indication**;**

1. *Venclexta is indicated for the treatment of relapsed or refractory chronic lymphocytic leukaemia (CLL) with 17p deletion.*
2. *Venclexta is indicated for the treatment of patients with relapsed or refractory CLL without the 17p deletion for whom there are no suitable treatment options.*

Note to indication. These indications are approved based on overall response rates. Duration of response and improvements in overall survival or health-related quality of life have not been established.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

- Subject to satisfactory implementation of the Risk Management Plan most recently negotiated by the TGA,
- The sponsor is required to present the results of the three studies described in the accelerated approval decision letter of the FDA to the TGA for evaluation as Category 1 submissions:
- Negotiation of Product Information and Consumer Medicines Information to the satisfaction of the TGA.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

Specific Advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *What is the opinion of the Committee regarding the population(s) in whom the efficacy and safety of venetoclax have been satisfactorily demonstrated to permit registration?*

The ACPM was of the view that, overall, the data are not especially robust as it is based on Phase I and II trials. However, the data that are available are positive and there is a need for additional therapies in CLL. It was noted that a Phase III trial is underway with results to be available in 2018.

In the relapsed/refractory CLL with 17p deletion population in particular, there is a medical need for better therapies. The results presented are impressive given the historically poor responses and look to fill a therapeutic gap in CLL therapy.

In the 'relapsed/refractory CLL without 17p deletion with no other suitable treatment options' population the data derive from dose-finding Phase I studies and one Phase II. However, these results also show very good early outcomes compared to what would be expected historically for standard immunochemotherapy. Positive updated PFS data are supplied, but investigator-assessed. The lack of available mature data has been addressed in the note to indication; with this note in place the ACPM recommended this indication for approval also.

2. *Given the un-randomised nature of the safety data, does the committee consider a black box warning necessary to warn for events of atypical infection?*

The ACPM advised against a boxed warning for atypical infection at this time. The overall incidence of these is not particularly high. In this population, atypical infection is not unexpected. The committee was of the view that the PI gives adequate information and recommendations.

The ACPM also noted that safety data will be continue to be collected and the RMP includes patient safety card (mainly for TLS) and an 'on-boarding' program for Haematologists.

3. *Does the Committee consider there should be any additional measures to enable prescribers to obtain informed consent and inform patients of potential risks of venetoclax therapy?*

The ACPM was of the view that patients having venetoclax therapy should be under specialist management only, given the lack of long-term data and need to manage tumour lysis closely. However, the committee assumed this would be the case in Australia for all patients.

The ACPM further advised that the proposed document named the 'Quick Start Guide' to be provided was inappropriate and it should be re-named the 'Safe Start Guide'.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Venclexta (venetoclax) 10 mg, 50 mg and 100 mg film-coated tablets for oral administration, indicated for:

Venclexta is indicated for the treatment of:

- *patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) with 17p deletion, or*
- *patients with relapsed or refractory CLL for whom there are no other suitable treatment options.*

Note to indications. The indications are approved based on overall response rates. Duration of response and improvements in overall survival, progression-free survival or health-related quality of life have not been established.

Specific conditions of registration applying to these goods

1. The Venetoclax EU-RMP(version 2.0, October 2016, data lock point 30 April 2015) with Australian Specific Annex (version 1.2, October 2016, which includes the provision of a patient alert card and quick start guide in the packaging), submitted with submission PM-2015-04328-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
2. The sponsor is required to present the results of the three studies as described in the accelerated approval decision letter of the FDA to the TGA for evaluation as Category 1 submissions:
    - § PMR # 3068-1: Submit the complete final report and data from ongoing trial GO28667, a randomized, Phase 3 trial comparing Venclexta (venetoclax) and rituximab with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia (CLL), including CLL with deletion 17p.
    - § PMR # 3068-2: Evaluate the effect of hepatic impairment on the pharmacokinetics and safety of Venclexta (venetoclax) compared to subjects with normal hepatic function. Submit a complete final report for trial M15-342 entitled, 'A Study to Evaluate the Safety and Pharmacokinetics of a Single Dose of Venetoclax in Female Subjects with Mild, Moderate, or Severe Hepatic Impairment.
    - § PMR # 3068-3: Evaluate the effect of Venclexta (venetoclax) co-administration on pharmacokinetics of a probe substrate of P-gp. Submit a complete final trial report.

Attachment 1. Product Information

The PI for Venclexta approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au