20 September 2018
EMA/CHMP/717206/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Venclyxto

International non-proprietary name: venetoclax

Procedure No. EMEA/H/C/004106/II/0011

Note

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

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AbbVie Limited submitted to the European Medicines Agency on 28 March 2018 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.13	Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	II and IIIB

Submission of the interim report from study M14-032 a phase II open-label study investigating efficacy and safety of venetoclax in patients with CLL with relapse or refractory to B-cell receptor signalling pathway inhibitor therapy, listed as a category 2 study in the RMP.

Consequently, the remaining SOB is fulfilled and Annex II E is updated accordingly.

The requested variation proposed amendments to the Annex II and Package Leaflet.

2. Overall conclusion and impact on the benefit/risk balance

Venetoclax received a conditional marketing authorization (EMEA/H/C/004106) in the EU on 05 December 2016. The current submission of the interim report of the Phase II Study M14-032 is towards the fulfilment of the Specific Obligation subject to which the conditional marketing authorization has been granted: "*In order to further confirm the efficacy and safety of venetoclax, the MAH should submit the clinical study report of study M14-032 investigating venetoclax in patients with chronic lymphocytic leukaemia relapsed after or refractory to treatment with B-cell receptor signalling pathway inhibitors*".

The basis to support efficacy of venetoclax in adult patients with chronic lymphocytic leukaemia (CLL) in the presence of 17p deletion or *TP53* mutations was the pivotal M13-982, where 106 patients (of a total 107) with del17p-CLL were enrolled in the main cohort.

In the submitted report of study M14-032 (a Phase II open-label study of the efficacy and safety of venetoclax in chronic lymphocytic leukemia subjects with relapse or refractory to B-cell receptor signaling pathway inhibitor therapy), patients who have previously received treatment with ibrutinib (n=91) and/or idelalisib (n=36), have relapsed on treatment, or experienced progression after discontinuation of either one of these agents were evaluated. Latest analysed efficacy outcomes (investigator assessed objective response rate (ORR) 65.4%; nodular partial remission (nPR) 2.4%; partial remission (PR) 52.8%) are consistent with earlier results (investigator assessed ORR 64%; nPR 3%; PR 52%). Independent Review Committee (IRC) assessed outcomes as of study cut-off date provided for a thorough assessment of efficacy. Progression-free survival (PFS) 12 months estimate is similar to original submitted data. Overall survival (OS) results are not yet mature but this is expected due to the chronic nature of the disease.
The safety profile presented in study M14-032 is consistent with known safety profile of venetoclax with diarrhoea, nausea, anaemia, and neutropenia among the most common Treatment Emergent Adverse Events (TEAEs).

Overall, data submitted confirmed the positive benefit/risk balance of Venclyxto in the approved indications. The submission of the present data fulfils the SOB and the CHMP was of the view that subject to the data submitted the dossier is now comprehensive. Therefore the CHMP recommends granting of a MA no longer subject to specific obligations.

Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.13	Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	I, II and IIIB

The Annex II is being updated following the fulfilment of Specific Obligation, which was requested to confirm the efficacy and safety of venetoclax in monotherapy, based on the assessment of interim study report of M14-032. In addition, section 5.1 of SmPC is being updated to reflect the updated results of Study M14-032. The Package Leaflet is updated accordingly.

Study M14-032 is: a phase II open-label study investigating efficacy and safety of venetoclax in patients with CLL with relapse or refractory to B-cell receptor signalling pathway inhibitor therapy, listed as a category 2 study in the RMP. The CHMP recommends granting of a marketing authorisation no longer subject to specific obligations.

☒ is recommended for approval.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

Amendments to the marketing authorisation

The following obligation has been fulfilled, and therefore it is recommended that it be deleted from the Annex II to the Opinion:

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

3. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Venclyxto-H-C-4106-II-11'.

4. Scientific discussion

4.1. Introduction

Venetoclax (also referred to as ABT-199 and GDC-0199) is a first-in-class, orally bioavailable, small-molecule B-cell lymphoma (Bcl)-2 family protein inhibitor in the biarylacylsulfonamide chemical class. Venetoclax is being developed jointly by AbbVie and Genentech Roche for the treatment of several haematological malignancies, including chronic lymphocytic leukaemia (CLL), non-Hodgkin's lymphoma, diffuse large B-cell lymphoma, multiple myeloma, acute myeloid leukaemia, and myelodysplastic syndrome.

The currently approved indication in the EU is:

"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."

Venetoclax was granted a conditional marketing authorisation pursuant to Article 14(7) of Regulation (EC) No 726/2004, by Commission Decision on 5 December 2016, subject to a specific obligation whereby the MAH was required to complete, within the stated timeframe, the following measures:

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

At the time of initial Marketing Authorisation of Venclyxto the MAH was required to provide further comprehensive clinical data to confirm efficacy and safety of venetoclax in the proposed indications with a specific focus on patients who had previously received ibrutinib or idelalisib as at the time of the venetoclax development these agents were being authorised and were not yet standard treatment. Therefore, the aim of the SOB from the efficacy perspective was to further confirm the efficacy of venetoclax in CLL patients who progressed on or after idelalisib or ibrutinib where patient numbers were low in the pivotal trial of the MAA. The updated M14-032 report was required to be submitted in 2018 (with number of subjects: n=124) providing longer term efficacy and safety follow up for original cohort (n=64) and a second, 60 patient cohort that has been added to the M14-032 protocol; of which 55 patients ((23 subjects with del 17p/TP53mut; 30 patients without del 17p/TP53mut) were enrolled at the time of Venclyxto approval. A complete 36 week response assessment for the second cohort was also required by CHMP.

These data were provided with the present submission of the interim report of trial M14-032 in line with the agreed deadline of March 2018.

The above measure is also listed as an additional pharmacovigilance activity category 2 in the risk management plan (RMP) with a due date of March 2018. Its purpose – in the context of the RMP - was to help address safety in long term exposure > 12 months and second primary malignancies and Richter's transformation in longer exposure to venetoclax.

The CHMP considered at the time of MA authorisation that this data will enable confirmation of benefit – risk in the target population of venetoclax.

At the time of market authorisation, study M14-032 intended to reach a median treatment duration of ≥24 months with data able to inform on exposure beyond 12 months. The interim study report was considered appropriate to fulfil the condition for the CMA. Final CSR was at that time to be anticipated by 2Q2019 and is expected to be submitted to CHMP for assessment.

The MAH states that this application is intended to fulfil the specific obligation [SOB] subject to which the conditional marketing authorization has been granted, and proposed deletion of the SOB from Annex II.E and an update to the package leaflet to remove reference to the conditional approval.

No RMP update was proposed with this variation. The RMP was assessed in a parallel submission (see procedure II/08).

5. Clinical Efficacy aspects

5.1. Methods – analysis of data submitted

Study M14-032 is fully enrolled but considered ongoing due to the fact that survival information will be collected up to 5 years after the last subject has been enrolled. A summary of the study as of 26 July 2017 is provided below. This is the interim report being submitted to satisfy the specific obligation.

Title of Study: A Phase II open-label study of the efficacy and safety of venetoclax (ABT-199/GDC-0199) in chronic lymphocytic leukaemia subjects with relapsed or refractory to B-cell receptor signalling pathway inhibitor therapy.

Protocol Phase of Study	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
5.3.5.2 Uncontrolled Clinical Studies						

M14-032 Phase II	To evaluate the efficacy and safety of venetoclax monotherapy in subjects with Chronic Lymphocytic Leukemia (CLL) relapsed after or refractory to treatment with B-cell Receptor Signaling Pathway Inhibitors. Efficacy will be measured by overall response rate (ORR).	Open-label, non-randomized, multicenter in 15 sites in the US	Venetoclax: Single daily doses QD starting with 20 mg; dose increments will proceed weekly → 50 mg → 100 mg → 200 mg → 400 mg as tolerated. Expansion Cohort subjects with bulky disease who are non-responders at the Week 12 Disease Assessment may be permitted to escalate venetoclax to 600mg dose.	n = 127 (43 in Arm A, 21 in Arm B and 63 in the Expansion Cohort)	Patients with R/R CLL after either Ibrutinib or Idelalisib treatments	Subjects may continue receiving study drug for up to 2 years following the date of the last subject enrolled provided they continue to tolerate the drug, have no evidence of disease progression, and do not meet any of the criteria for subject discontinuation.

One hundred twenty-seven subjects in Study M14-032 were enrolled with a median duration of venetoclax exposure of 14.3 (range: 0.1 – 31.4) months. All subjects in the main cohort crossed the 24-week assessment. All subjects in the expansion cohort had the 36-week assessment. Median study follow-up was 16.9 months.

The primary efficacy endpoint, objective response rate (ORR), was calculated for all subjects in Study M14-032 based on International Workshop for Chronic Lymphocytic Leukemia (IWCLL) National Cancer Institute-Working Group (NCI-WG) criteria.

5.2. Results

The majority of subjects enrolled in the study were white (92.1%) and male (70.1%). The median number of prior oncology regimens was 4 (range 1 to 15). The subjects ranged in age from 28 to 85 years of age (median: 66 years). At screening, a total of 52 subjects (40.9%) had one or more nodes ≥ 5 cm; 14 subjects (11.0%) had one or more nodes ≥ 10 cm.

Table 1: Objective Response Rates – Investigator Assessment

	Ibrutinib Failure Total N = 91		Idelalisib Failure Total N = 36		All Subjects N = 127	
Subject Response[a]	**n (%)**	**[95% CI]**	**n (%)**	**[95% CI]**	**n (%)**	**[95% CI]**
Objective response rate (CR + CRi + nPR + PR)	59 (64.8)	[54.1, 74.6]	24 (66.7)	[49.0, 81.4]	83 (65.4)	[56.4, 73.6]
Complete remission rate (CR + CRi)	9 (9.9)	[4.6, 17.9]	4 (11.1)	[3.1, 26.2]	13 (10.2)	[5.6, 16.9]
Partial remission rate (nPR + PR)	50 (54.9)	[44.2, 65.4]	20 (55.6)	[38.1, 72.1]	70 (55.1)	[46.0, 63.9]
Nodular partial remission	3 (3.3)		0		3 (2.4)	
Partial remission	47 (51.6)		20 (55.6)		67 (52.8)	
Stable Disease	21 (23.1)		10 (27.8)		31 (24.4)	
Disease Progression	5 (5.5)		2 (5.6)		7 (5.5)	
Incomplete Data	6 (6.6)		0		6 (4.7)	

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 as of 26 July 2017.

Note: Investigator assessments were performed in the Main Cohort at Weeks 8, 24, and every 12 weeks thereafter for 1 year; and in the Expansion Cohort at Weeks 12, 36, and 48.

Table 2: Objective Response Rates – Independent Review Committee Assessment

	Total Ibrutinib Failure (N = 91)		Total Idelalisib Failure(N = 36)		All Subjects (N = 127)	
Subject Response[a]	**n (%)**	**[95% CI]**	**n (%)**	**[95% CI]**	**n (%)**	**[95% CI]**
ORR (CR + CRi + nPR + PR)	64 (70.3)	[59.8, 79.5]	25 (69.4)	[51.9, 83.7]	89 (70.1)	[61.3, 77.9]
CR rate (CR + CRi)	1 (1.1)	[0.0, 6.0]	0		1 (0.8)	[0.0, 4.3]
PR rate (nPR + PR)	63 (69.2)	[58.7, 78.5]	25 (69.4)	[51.9, 83.7]	88 (69.3)	[60.5, 77.2]
nPR	0		0		0	
PR	63 (69.2)		25 (69.4)		88 (69.3)	
Nonresponder[b]	23 (25.3)		11 (30.6)		34 (26.8)	
Not assessed	4 (4.4)		0		4 (3.1)	

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; ORR = objective response rate; PR = partial remission

a. Data are as of 26 July 2017.
b. Subjects with progressive disease, stable disease, or incomplete data were considered non-responders by the IRC.
Note: IRC assessments were performed at Week 24 for the Main Cohort and Week 36 for the Expansion Cohort.

Key secondary efficacy endpoints included duration of response (DOR), progression-free survival (PFS), time to progression (TTP), and overall survival (OS), and were calculated for all subjects in Study M14-032. The Kaplan-Meier estimates of DOR at 12 months for total ibrutinib failure subjects and total idelalisib failure subjects were 86.4% (95% confidence interval (CI): 73.5%, 93.3%) and 90.2% (95% CI: 66.2%, 97.5%), respectively. The median duration of PFS is 24.7 months in ibrutinib failure total cohort, and was not reached in the idelalisib failure total cohort. Per investigator assessment, median time to first response for all subjects was 2.5 months (range: 1.6 to 14.9 months).The Kaplan-Meier estimate for OS for all subjects at 12 months was 92.0% (95% CI: 85.6%, 95.6%) and was similar between total ibrutinib failure and total idelalisib failure subjects.

Table 3: Summary of Progression-Free Survival – Investigator Assessment

	Subjects with Objective Response		
	Ibrutinib Failure Total N = 91	Idelalisib Failure Total N = 36	All subjects N = 127
Number of Subjects, n (%)			
With events	34 (37.4)	11 (30.6)	45 (35.4)
Without an event	57 (62.6)	25 (69.4)	82 (64.6)
Median[a] [95% CI]	24.7 [19.2, -]	NR [16.4, -]	24.7 [19.6, -]
Estimate [95% CI]			
At Month 12	75.4 [64.7, 83.2]	80.4 [63.1, 90.1]	76.8 [68.1, 83.4]
At Month 18	65.3 [53.2, 75.1]	67.0 [46.2, 81.2]	65.6 [55.3, 74.1]
At Month 24	51.0 [36.3, 63.9]	61.4 [39.6, 77.4]	53.9 [41.8, 64.6]

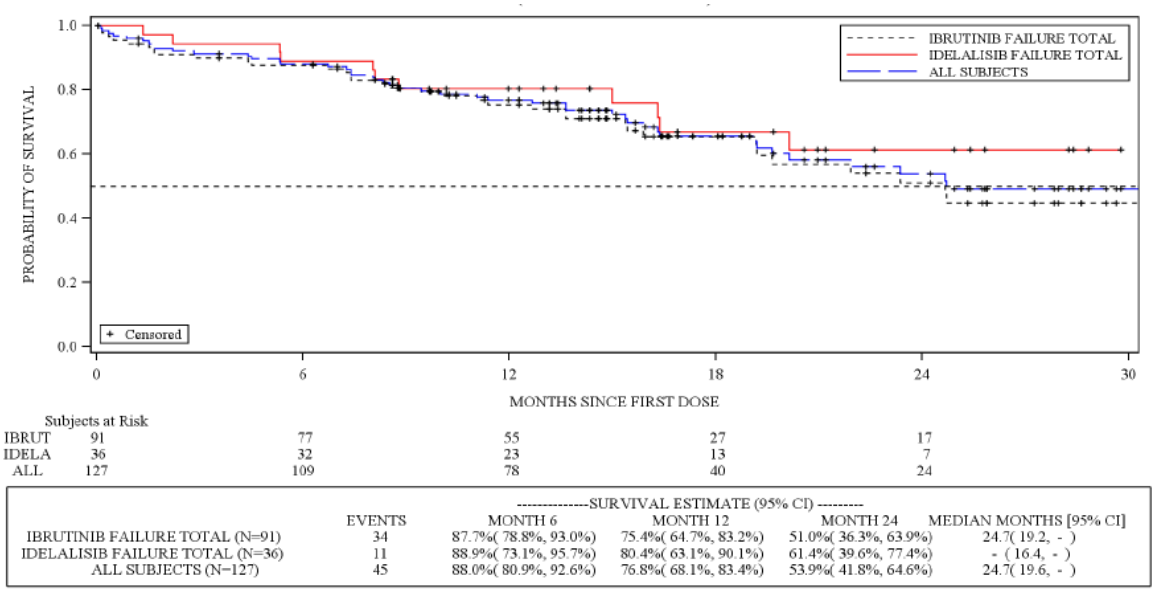
CI = confidence interval; NR = not reached
a. Data are in months.

Table 4: Summary of Duration of Progression-free Survival – Assessed by Independent Review Committee

	Ibrutinib Failure Total N = 91 n (%)	Idelalisib Failure Total N = 36 n (%)	All subjects N = 127 n (%)
NUMBER OF SUBJECTS WITH EVENTS	16(17.6%)	5(13.9%)	21(16.5%)
EARLIEST CONTRIBUTION EVENT			
DISEASE PROGRESSION	12	4	16
DEATH	4	1	5
NUMBER OF SUBJECTS WITHOUT AN EVENT	75(82.4%)	31(86.1%)	106(83.5%)
DURATION OF PROGRESSION-FREE SURVIVAL (MONTHS)			
25TH (95% CI)	13.2(6.0, -)	- (5.4, -)	13.2(8.8, -)
50TH (95% CI)	- (13.2, -)	- (8.8, -)	- (13.2, -)
75TH (95% CI)	- (13.2, -)	- (- , -)	- (13.2, -)
PFS ESTIMATE AT MONTH 6 (95% CI)	85.9%(76.5%, 91.7%)	87.9%(70.8%, 95.3%)	86.5%(78.9%, 91.5%)
PFS ESTIMATE AT MONTH 12 (95% CI)	81.7%(71.5%, 88.6%)	NA	81.1%(71.5%, 87.7%)
PFS ESTIMATE AT MONTH 18 (95% CI)	NA	NA	NA
PFS ESTIMATE AT MONTH 24 (95% CI)	NA	NA	NA

NOTE: PROGRESSION-FREE SURVIVAL IS DEFINED AS THE NUMBER OF MONTHS FROM THE DAY THE SUBJECT STARTED STUDY DRUG TO EITHER AN EVENT OF DISEASE PROGRESSION OR DEATH.

Figure 1: Kaplan-Meier Duration of Progression-Free Survival (Investigator Assessment): Ibrutinib and Idelalisib Failure Totals



		SURVIVAL ESTIMATE (95% CI)			
	EVENTS	MONTH 6	MONTH 12	MONTH 24	MEDIAN MONTHS [95% CI]
IBRUTINIB FAILURE TOTAL (N=91)	34	87.7%(78.8%, 93.0%)	75.4%(64.7%, 83.2%)	51.0%(36.3%, 63.9%)	24.7(19.2, -)
IDELALISIB FAILURE TOTAL (N=36)	11	88.9%(73.1%, 95.7%)	80.4%(63.1%, 90.1%)	61.4%(39.6%, 77.4%)	- (16.4, -)
ALL SUBJECTS (N=127)	45	88.0%(80.9%, 92.6%)	76.8%(68.1%, 83.4%)	53.9%(41.8%, 64.6%)	24.7(19.6, -)

Table 5: Summary of Overall Survival

	Ibrutinib Failure Total N = 91 n (%)	Idelalisib Failure Total N = 36 n (%)	All subjects N = 127 n (%)
NUMBER OF SUBJECTS WHO DIED	18 (19.8%)	4 (11.1%)	22 (17.3%)
NUMBER OF SUBJECTS STILL ALIVE	73 (80.2%)	32 (88.9%)	105 (82.7%)
DURATION OF OVERALL SURVIVAL (MONTHS)			
25TH (95% CI)	22.1 (17.5, -)	- (16.2, -)	27.8 (18.5, -)
MEDIAN (95% CI)	- (-, -)	- (-, -)	- (-, -)
75TH (95% CI)	- (-, -)	- (-, -)	- (-, -)
ESTIMATE AT MONTH 6 (95% CI)	93.3%(85.7%, 96.9%)	97.2%(81.9%, 99.6%)	94.4%(88.7%, 97.3%)
ESTIMATE AT MONTH 12 (95% CI)	91.0%(82.8%, 95.4%)	94.2%(78.6%, 98.5%)	92.0%(85.6%, 95.6%)
ESTIMATE AT MONTH 18 (95% CI)	83.7%(72.5%, 90.6%)	89.9%(71.2%, 96.7%)	85.5%(76.8%, 91.2%)
ESTIMATE AT MONTH 24 (95% CI)	71.5%(56.9%, 81.9%)	84.9%(63.6%, 94.3%)	75.3%(63.7%, 83.6%)

NOTE: OVERALL SURVIVAL IS DEFINED AS THE NUMBER OF MONTHS FROM THE DATE OF FIRST DOSE TO THE DATE OF DEATH.

The above data for the primary and secondary end points is consistent with data submitted as part of the initial Marketing Authorization Application (MAA) review.

Table 6: Efficacy results as assessed by investigator in patients who have failed a B-cell receptor pathway inhibitor (Study M14-032)

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

The efficacy data were further evaluated by an IRC demonstrating a combined ORR of 70% (Arm A: 70%; Arm B: 69%). One patient (ibrutinib failure) achieved complete remission with incomplete marrow recovery. The ORR for patients with 17p deletion and/or *TP53* mutation was 72% (33/46) (95% CI: 56.5, 84.0) in Arm A and 67% (8/12) (95% CI: 34.9, 90.1) in Arm B. For patients without 17p deletion and/or *TP53* mutation, the ORR was 69% (31/45) (95% CI: 53.4, 81.8) in Arm A and 71% (17/24) (95% CI: 48.9, 87.4) in Arm B.

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

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

5.3. Discussion

Study M14-032, an open-label, multi-center, non-randomised phase II trial in patients with CLL who had been previously treated with and failed ibrutinib or idelalisib therapy - is now fully enrolled. The study is still ongoing due to planned 5-year survival follow up but more mature data (compared to previous submissions) are presented regarding several efficacy endpoints.

At the time of data cut-off (26 July 2017), 127 patients were enrolled and treated with venetoclax. Of these, 91 patients had received prior ibrutinib therapy (Arm A) and 36 had received prior idelalisib therapy (Arm B). The median age was 66 years (range: 28 to 85 years), 70% were male, and 92% were white. The median time since diagnosis was 8.3 years (range: 0.3 to 18.5 years; N=96). Chromosomal aberrations were 11q deletion (34%, 43/127), 17p deletion (40%, 50/127), *TP53* mutation (38%, 26/127) and unmutated *IgVH* (78%, 72/127). At baseline, 41% of patients had one or more nodes ≥5 cm and 31% had ALC ≥25 x 10^9/l. The median number of prior oncology treatments was 4 (range: 1 to 15) in ibrutinib-treated patients and 3 (range: 1 to 11) in idelalisib-treated patients. Overall, 65% of patients received prior nucleoside analogue, 86% rituximab, 39% other monoclonal antibodies, and 72% alkylating agent (including 41% with bendamustine). At the time of evaluation, median duration of treatment with venetoclax was 14.3 months (range: 0.1 to 31.4 months).

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

The efficacy data were further evaluated by an IRC demonstrating a combined ORR of 70% (Arm A: 70%; Arm B: 69%). One patient (ibrutinib failure) achieved complete remission with incomplete marrow recovery. The ORR for patients with 17p deletion and/or *TP53* mutation was 72% (33/46) (95% CI: 56.5, 84.0) in Arm A and 67% (8/12) (95% CI: 34.9, 90.1) in Arm B. For patients without 17p deletion and/or *TP53* mutation, the ORR was 69% (31/45) (95% CI: 53.4, 81.8) in Arm A and 71% (17/24) (95% CI: 48.9, 87.4) in Arm B.

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

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

At the time of the MAA data cut-off, 64 patients were enrolled and treated with venetoclax. Of these, 43 patients had received prior ibrutinib therapy (Arm A) and 21 had received prior idelalisib therapy

(Arm B). Of the patients, 91% (39/42) in Arm A had relapsed on or were refractory to ibrutinib and 67% (14/21) in Arm B had relapsed on or were refractory to idelalisib. The primary efficacy endpoint was ORR according to IWCLL updated NCI-WG guidelines was 67% with CR at 7%.

The updated efficacy results, as presented by the MAH above, are in line with, or slightly more positive, than previous presented efficacy results. Investigator assessed ORR was initial 64% and at latest data cut-off 65.4%. CR + CRi has changed from 9% to 10.2% (0.8% IRC assessed) and 12 months PFS estimate has changed from 72% to 76.8% (81.1% IRC assessed). PFS estimate beyond 12 months declines, but not unexpectedly and at 18 months there are still a sufficient number of patients in the analysis whereas data become more immature at the 24 months estimate. The SmPC has been updated to include updated efficacy data from Study M14-032 as of 26 July 2017 data cutoff (see SmPC point 5.1).

6. Clinical Safety aspects

6.1. Methods – analysis of data submitted

As of 26 July 2017, 127 subjects in Study M14-032 were enrolled with a median duration of venetoclax exposure of 14.3 (range: 0.1 – 31.4) months. A total of 59 subjects discontinued venetoclax, including 7 subjects who discontinued venetoclax during ramp-up. The most common primary reasons for study discontinuation were progressive disease (35 subjects, including 6 subjects with Richter's transformation), AEs related to progression (2 subjects), AEs not related to progression (7 subjects), and stem cell transplant (6 subjects).

6.2. Results

Table 7: Overview of Treatment-Emergent Adverse Events – Study M14-032

Subjects with:	**Total Ibrutinib Failure N = 91 n (%)**	**Total Idelalisib Failure N = 36 n (%)**	**Total N = 127 n (%)**
Any AE	91 (100)	36 (100)	127 (100)
NCI toxicity grade ≥ 3	77 (84.6)	28 (77.8)	105 (82.7)
NCI toxicity grade 3 or 4	77 (84.6)	28 (77.8)	105 (82.7)
Reasonable possibility related to venetoclax[a]	75 (82.4)	31 (86.1)	106 (83.5)
SAE	48 (52.7)	16 (44.4)	64 (50.4)
AEs leading to			
Study discontinuation	14 (15.4)	1 (2.8)	15 (11.8)
Venetoclax discontinuation	14 (15.4)	1 (2.8)	15 (11.8)
Venetoclax discontinuation – disease	7 (7.7)	1 (2.8)	8 (6.3)
Venetoclax discontinuation – not disease	7 (7.7)	0	7 (5.5)
Venetoclax interruption	35 (38.5)	15 (41.7)	50 (39.4)
Venetoclax reduction	11 (12.1)	6 (16.7)	17 (13.4)
Fatal AE	6 (6.6)	1 (2.8)	7 (5.5)

All deaths[b]	18 (19.8)	4 (11.1)	22 (17.3)

AE = adverse event; NCI = National Cancer Institute; SAE = serious adverse event

a. As assessed by investigator.
b. Includes non-treatment-emergent deaths
Data are as of 26 July 2017.

The most common TEAEs, regardless of severity or relationship to study drug, were diarrhoea (49.6%), nausea (48.8%), anaemia (43.3%), and neutropenia (40.2%). Grade 3 or 4 AEs were reported in 82.7% of the subjects. The most common grade 3 or 4 TEAEs, regardless of relationship to study drug, are listed by prior treatment failure below:

- Ibrutinib Failure Total: neutropenia (30.8%), anaemia (29.7%), and neutrophil count decreased (26.4%).
- Idelalisib Failure Total: neutropenia (44.4%), thrombocytopenia (19.4%), and anaemia (16.7%).

The most common of TEAEs that led to venetoclax dose interruption were diarrhoea (7.1%) and pneumonia (4.7%).

Treatment-related adverse events were reported in 83.5% of subjects. The most common venetoclax-related adverse events in these subjects were neutropenia (31.5%), diarrhoea (27.6%), and nausea (26.8%).

Table 8: Serious Adverse Events Occurring in > 1 Subject

	Number of Subjects (%)		
System Organ Class MedDRA 20.1 Preferred Term	**Ibrutinib Failure Total N = 91**	**Idelalisib Failure Total N = 36**	**All Subjects N = 127**
Any adverse event	48 (52.7)	16 (44.4)	64 (50.4)
Blood and lymphatic system disorders	15 (16.5)	1 (2.8)	16 (12.6)
Autoimmune haemolytic anaemia	2 (2.2)	0	2 (1.6)
Febrile neutropenia	11 (12.1)	1 (2.8)	12 (9.4)
Gastrointestinal disorders	7 (7.7)	1 (2.8)	8 (6.3)
Small intestinal obstruction	2 (2.2)	0	2 (1.6)
General disorders and administration site conditions	8 (8.8)	3 (8.3)	11 (8.7)
Fatigue	1 (1.1)	1 (2.8)	2 (1.6)
Multiple organ dysfunction syndrome	1 (1.1)	1 (2.8)	2 (1.6)
Pyrexia	2 (2.2)	0	2 (1.6)
Immune system disorders	2 (2.2)	0	2 (1.6)
Cytokine release syndrome	2 (2.2)	0	2 (1.6)
Infections and infestations	18 (19.8)	9 (25.0)	27 (21.3)
Cellulitis	2 (2.2)	0	2 (1.6)
Pneumonia	5 (5.5)	2 (5.6)	7 (5.5)
Pneumonia bacterial	1 (1.1)	1 (2.8)	2 (1.6)

Septic shock	1 (1.1)	1 (2.8)	2 (1.6)
Investigations	3 (3.3)	1 (2.8)	4 (3.1)
Blood potassium increased	2 (2.2)	1 (2.8)	3 (2.4)
Metabolism and nutrition disorders	7 (7.7)	1 (2.8)	8 (6.3)
Dehydration	2 (2.2)	0	2 (1.6)
Hypercalcaemia	2 (2.2)	1 (2.8)	3 (2.4)

MedDRA = Medical Dictionary for Regulatory Activities

Based on cumulative safety data for venetoclax to date, the following adverse events of special interest have been closely monitored: tumour lysis syndrome (TLS), neutropenia, and serious infections.

Of the 8 subjects identified as meeting Howard Criteria for laboratory TLS (LTLS), 2 subjects were identified as having LTLS during medical review, both with high tumor burden. Six subjects identified for meeting Howard criteria had confounding factors: 4 of these subjects had confounding factors due to other medical events and 2 of these subjects had electrolyte changes before administration or after discontinuation of venetoclax.

Overall, the updated data from Study M14-032 continue to demonstrate that 400 mg venetoclax was well tolerated, and the available safety profile is comparable to that observed in the overall venetoclax monotherapy CLL clinical programme.

With regards to the RMP category 2 commitments, the current data do not confirm a contributory role of venetoclax to the events of second primary malignancies or Richter's transformation. These two potential safety concerns will continue to be monitored using a number of other ongoing monotherapy studies as outlined in the current RMP as well as the non- interventional Prospective Observational Study to Assess the Long Term Safety Profile of Venetoclax in a Swedish cohort of CLL patients (Protocol P16-562), agreed by CHMP 25th January 2018.

In the SmPC the following tabulated list of adverse reactions is available:

Table 9: Adverse drug reactions reported in patients with CLL treated with venetoclax

System organ class	*Frequency (all grades)*	*Adverse reactions (N=296)*
Infections and infestations	*Very common*	*Upper respiratory tract infection*
	Common	*Pneumonia* *Urinary tract infection*
Blood and lymphatic system disorders	*Very common*	*Neutropenia*
		Anaemia
	Common	*Febrile neutropenia*
		Lymphopenia
Metabolism and nutrition disorders	*Very common*	*Hyperphosphataemia*
	Common	*Tumour lysis syndrome* *Hyperkalaemia* *Hyperuricaemia* *Hypocalcaemia*
Gastrointestinal disorders	*Very common*	*Diarrhoea* *Vomiting* *Nausea* *Constipation*
General disorders and administration site conditions	*Very common*	*Fatigue*
Investigations	*Common*	*Blood creatinine increased*

Tumour lysis syndrome

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

In 122 patients with CLL starting with a daily dose of 20 mg and increasing over 5 weeks to a daily dose of 400 mg, the rate of TLS was 3%.

In addition the MAH was requested to provide further information on IRC assessed efficacy from the same data cut off time Table 7 in the SmPC.

Table including IRC assessment from initial MAA (10 June 2016) and from updated evaluation 26 July 2017 is presented below:

Table 10: IRC assessed efficacy from the same data cut off time as Table 7 in SmPC

	IRC Assessed n (%) [95% CI]			
	Arm A Ibrutinib Failure		**Arm B Idelalisib Failure**	
	26 July 2017 (N = 91)	**10 June 2016 (N=43)**	**26 July 2017 (N = 36)**	**10 June 2016 (N=21)**
ORR (CR + CRi + nPR + PR)	64 (70.3)	30 (69.8)	25 (69.4)	13 (61.9)
[95% CI]	[59.8, 79.5]	[53.9, 82.8]	[51.9, 83.7]	[38.4, 81.9]
CR rate (CR + CRi)	1 (1.1)	0 + 1 (2.3)	0	0
[95% CI]	[0.0, 6.0]	NA		NA
PR rate (nPR + PR)	63 (69.2)	NA	25 (69.4)	NA
[95% CI]	[58.7, 78.5]	NA	[51.9, 83.7]	NA
nPR	0	0	0	0
PR	63 (69.2)	29 (67.4)	25 (69.4)	13 (61.9)
Nonresponder[a]	23 (25.3)	13 (30.2)	11 (30.6)	8 (38.1)
Not assessed	4 (4.4)	NA	0	NA

CI = confidence interval (95% CI is from the exact binomial distribution); CR = complete remission; CRi = complete remission with incomplete marrow recovery; IRC = Independent Review Committee; nPR = nodular partial remission; ORR = objective response rate; PR = partial remission

a. Subjects with progressive disease, stable disease, or incomplete data were considered non-responders by the IRC.
Note: IRC assessments were performed at Week 24 for the Main Cohort and Week 36 for the Expansion Cohort.

Table constructed from Table 1 in MAH answer + Table 2 in AR (above)

6.3. Discussion

The MAH presented a comprehensive safety report including presentation of the individual study data as well as integrated safety data. Reported frequency of TEAEs and common SAEs in study M14-032 are consistent with frequencies described in SmPC. No new safety concerns have been described.

IRC assessment of responses does not change significantly between previous and more recent evaluation. The differences are not considered clinical significant.

The safety profile presented in study report M14-032 does not change benefit / risk balance of Venclyxto in approved indications.

The MAH will discuss and update section 4.8 of the SmPC with updated safety analysis of studies: M14-032, M12-175 and M13-982 in the context of another procedure currently under assessment in order to reflect the most up to safety information from each study.

7. Changes to the Product Information

As a result of this variation, Annex II has been updated to remove the SOB.

Furthermore, upon request by the CHMP, the MAH has updated SmPC section 5.1 to include the latest efficacy analyses from study M14-032. The package leaflet was also updated to remove reference to the conditional approval.

Safety information will be included in the SmPC 4.8, as combined safety data from multiple studies in the context of an ongoing variation.

8. Attachments

1. Product Information as adopted by CHMP on 20th September 2018.