Amsterdam, 14 December 2023
EMA/25886/2024
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Venclyxto

Venetoclax

Procedure no: EMEA/H/C/004106/P46/018

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	2023-10-16	2023-10-16	☐
☐	CHMP Rapporteur Assessment Report	2023-11-20	2023-11-17	☐
☐	CHMP members comments	2023-12-04	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	2023-12-07	n/a	☐
☒	CHMP adoption of conclusions:	2023-12-14	2023-12-14	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Declarations

☒ The assessor confirms that this assessment does **not** include non-public information, including commercially confidential information (e.g. ASMF, information shared by other competent authorities or organisations, reference to on-going assessments or development plans etc), irrespective from which entity was received*.

**If the entity from which non-public information originates has consented to its further disclosure, the box should be ticked and there* would *be no need to add details below.*

Whenever the above box is un-ticked please indicate section and page where confidential information is located here:

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1. Introduction

On 2 October 2023, the MAH submitted a completed paediatric study for venetoclax, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are submitted as part of the post-authorisation measure. A short critical expert overview has also been provided.

The MAH does not propose an update of the product information.

2. Scientific discussion

2.1. Information on the development program

The MAH has submitted the final clinical study report for study M13-833 as a stand-alone submission in accordance with Article 46 of Regulation (EC) No. 1901/2006.

The MAH stated that study M13-833 is part of a clinical development program and is included in the Venetoclax Paediatric Investigation Plan (EMEA-002018-PIP02-16-M05) as Study 3.

A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

Table 1. Identity of investigational product

Study Drug	Dosage Form	Formulation	Manufacturer	Bulk Lot
Venetoclax (ABT-199) Formulation 2 Lake County	Suspension	2.5 mg tablet for oral suspension	AbbVie	16-003195 1000299666 1000466117
Venetoclax (ABT-199) Formulation 2 Lake County	Suspension	10 mg tablet for oral suspension	AbbVie	16-003196 1000234763 1000371463 1000429263
Venetoclax (ABT-199) Formulation 2 Lake County	Suspension	25 mg tablet for oral suspension	AbbVie	16-003197 1000211039 1000211044 1000208844 1000234773 1000211045 1000374492 1000371462 1000380707 1000383429 1000465246
Venetoclax A-1195425.0 (ABT-199) Genotoxic	Tablet	10 mg Yellow Film-Coated Tablet	AbbVie	17-008165 1000220684 1000317832 1000405517
Venetoclax A-1195425.0 (ABT-199) Genotoxic	Tablet	50 mg Beige Film-Coated Tablet	AbbVie	17-008166 1000220683 1000247247 1000282570 1000358214 1000404061 1000482733
Venetoclax A-1195425.0 (ABT-199) Genotoxic	Tablet	100 mg Yellow Film-Coated Tablet	AbbVie	1000205342 1000216759 1000261206 1000254284 1000278136 1000346625 1000373027 1000212171

2.3. Clinical aspects

2.3.1. Introduction

Venetoclax (tradename Venclyxto) is a selective, orally bioavailable, small molecule B-cell lymphoma-2 (BCL-2) inhibitor.

In the EU, Venclyxto is approved in the following indications:

- Venclyxto in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) (see section 5.1).
- Venclyxto in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.

- Venclyxto monotherapy is indicated for the treatment of CLL:
  - in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or
  - in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.
- Venclyxto in combination with a hypomethylating agent is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.

With this procedure the MAH submitted the final report for study M13-833, a Phase 1 study of the safety and pharmacokinetics (PK) of venetoclax in paediatric and young adult patients with relapsed or refractory malignancies.

2.3.2. Clinical study

Study M13-833

Description

Study M13-833 was an open-label, global, Phase 1, dose determination (consisting of both a dose determination and dose escalation/de-escalation component) and cohort expansion study in pediatric and young adult subjects with relapsed or refractory malignancies.

Study design

In Part 1, Dose Determination subjects with any relapsed or refractory tumor without available curative treatment options were eligible to enroll. In Part 1, Dose Escalation/De-escalation solid tumor subjects without bone marrow involvement were eligible to enroll. During Part 2 (Cohort Expansion), subjects were enrolled into one of five tumor cohorts. Four of the cohorts enrolled subjects with the following malignancies: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), non-Hodgkin lymphoma (NHL), or Neuroblastoma (NBL). A fifth exploratory cohort (referred to as Other Tumors) enrolled subjects with any other tumor that expressed B-cell lymphoma-2 (BCL-2) or subjects with transcription factor 3-hepatic leukemia factor (TCF3-HLF) ALL confirmed during frontline induction therapy. Subjects who had primary brain tumors and disease that was metastatic to the brain were excluded because of preclinical murine data indicating that venetoclax is unlikely to penetrate a mature blood-brain barrier. Subjects with solid tumors enrolled in the fifth cohort were analyzed separately.

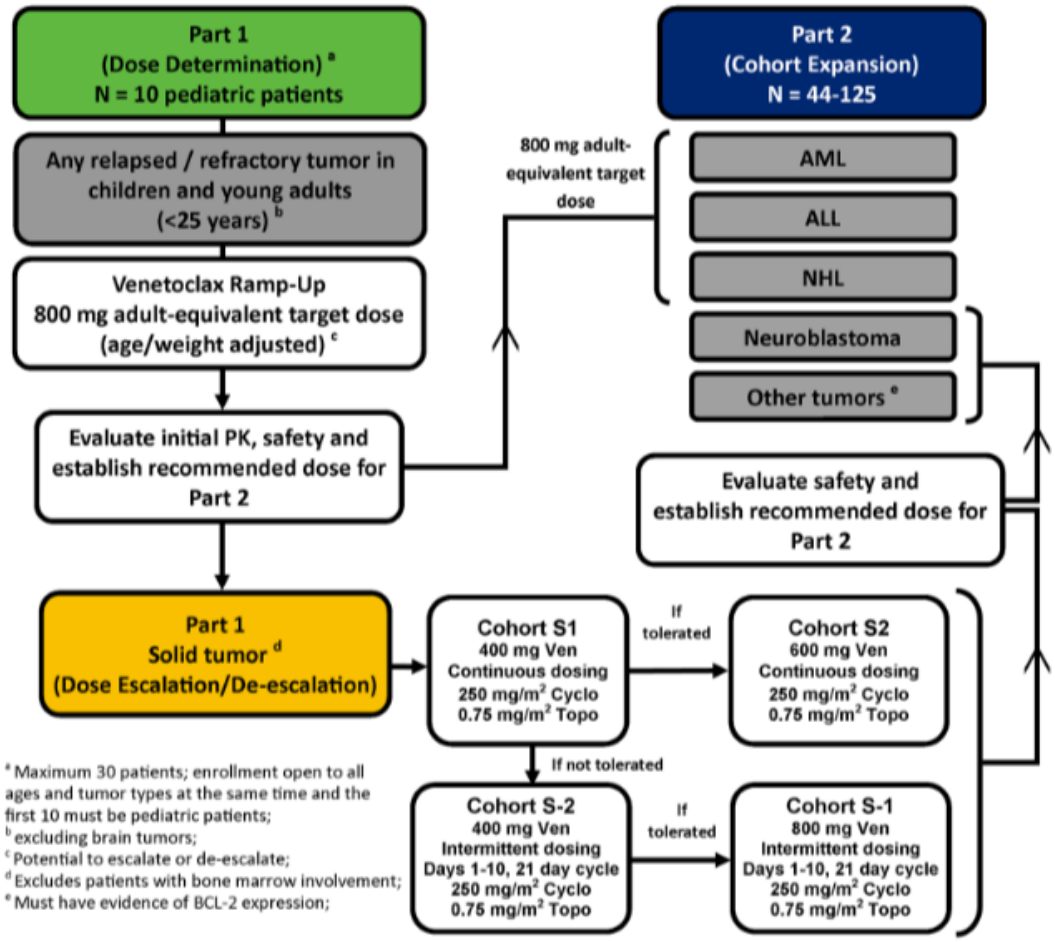


Figure 1 Study Design Schematic

Methods

Study participants

In summary the study planned to enroll 165 patients (whereas 143 were actually enrolled, 140 were analyzed).

Part 1 will enroll a minimum of 10 patients with any relapsed or refractory tumor type without available curative treatment options. Approximately 45 patients may be enrolled to ensure sufficient enrolment across age and weight ranges and tumor types if additional PK data is required.

Part 2 will enroll 44 – 125 patients into five tumor cohorts. ALL, AML, NHL and neuroblastoma comprise four of these cohorts.

Diagnosis and main criteria for inclusion:

- Subjects were <25 years of age.
  o Enrollment of subjects ≥18 years of age was halted at any time during the study to ensure adequate enrollment of pediatric subjects (<18 years).
- Subjects had relapsed or refractory cancer.
  o Subjects with high-risk neuroblastoma that was refractory after completion of at least 4 cycles of induction therapy (no response or stable disease as best response) were eligible to enroll in Part 2 (cohort expansion).

o Subjects with confirmed diagnosis of TCF3-HLF ALL were eligible to enroll in the 5th cohort in Part 2 (cohort expansion) beginning on or after Day 15 of induction or the end of induction and were assessed independently of other subjects with ALL.

- Subjects had adequate hepatic function.
- Subjects had normal creatinine for age or have a calculated creatinine clearance ≥60 mL/min/1.73 m^2.
- Subjects ≤16 years of age had performance status of Lansky ≥50% and subjects >16 years of age had performance status of Karnofsky ≥50%.
- In Part 1, subjects with solid tumors (with the exception of neuroblastoma) had adequate bone marrow function as defined by absolute neutrophil count (ANC) ≥1000/μL and platelets >75,000/μL (with transfusion independence defined as not receiving platelet transfusion within 7 days prior to enrollment).
- For Part 2 of the study – for enrollment into the fifth cohort (other tumors), subjects had evidence of BCL-2 expression determined locally in either archived tumor tissue or tumor tissue available at relapse. Exception: subjects with TCF3-HLF ALL enrolled in the fifth cohort were not required to have evidence of BCL-2 expression.

Treatments

This was an open-label Phase 1 study without any active- or placebo control group(s). An overview of the different test product formulations is shown in Table 1 (section 2.2).

Venetoclax was administered orally QD, continuously, in subjects with hematologic malignancies. Subjects with Solid Tumors enrolled in Part 1 (Dose Determination) were also administered venetoclax orally QD, continuously. Subjects with Solid Tumors enrolled in the Escalation/De-escalation portion of Part 1 were administered venetoclax orally QD, continuously or intermittently depending on the assigned cohort.

Venetoclax dose was ramped up to the target dose over 2 or 3 days depending on the tumor type. Subjects with Solid Tumors were ramped up over 2 days (400 mg Day 1 – 800 mg Day 2) and Subjects with liquid tumors (ALL, AML, NHL) were ramped up over 3 days (200 mg Day 1 – 400 mg Day 2 – 800 mg Day 3).

Patients who are <2 years of age were to be dosed based on age because venetoclax is metabolized through the CYP3A system, which is not fully mature until the age of 2. Patients who are 2 years of age and older were to be dosed based on weight.

Individual doses will be adjusted by age or weight to match an adult exposure equivalent target daily dose of 800 mg. During Part 1 (Dose Determination), all patients will be administered the tablet for oral suspension (see Table 2: Venetoclax Dosing). If 800 mg is not tolerated, a lower dose (400 mg adult equivalent) will be evaluated at a lower dose level. Dose levels greater than 800 mg may be evaluated. At start of treatment, venetoclax will ramp-up to the target dose over 3 days (equivalent to 200 mg Day 1 – 400 mg Day 2 – 800 mg Day 3; see Table 2: Venetoclax Dosing Day 3). The maximum tolerated dose for venetoclax monotherapy has not been reached in adult studies evaluating daily venetoclax monotherapy at doses up to 1200 mg. Doses will be adjusted if needed based on PK data from Part 1 (Dose Determination).

Table 2 Venetoclax dosing for Patients with Hematologic Malignancies or Lymphomas. The table shows the 800 mg adult-equivalent target dose of venetoclax at the third and final day of Ramp-up

Dose Groups: Age Weight	Day 1	Day 2	Day 3 and Onwards (mg)
newborn – < 1 month	2.5*	5*	10
1 – < 3 months	5*	10	25*
3 – < 6 months	10	25*	50
6 months – < 1 year	25*	50	100
1 – < 2 years	40	80	150
10 – < 20 kg	50	120	250
20 – < 30 kg	80	170	350
30 – < 45 kg	120	250	500
≥ 45 kg	200	400	800

* Dose can only be administered using the tablet for oral suspension formulation.

The recommended dose for cohort expansion was chosen based on evaluation of the 800 mg dose during Part 1 and if required, evaluation of a dose lower or higher than 800 mg. The stepwise dosing to 800 mg may be eliminated during Part 2, following analysis of data generated during Part 1.

Patients could receive study drug up to 9 months.

Venetoclax in combination with chemotherapy

Combination with chemotherapy was allowed on Day 3/Day 4 or later as decided by the investigator.

Chemotherapy was added to venetoclax beginning on Day 4 for subjects with liquid tumors and beginning on Day 3 for subjects with neuroblastoma or solid tumors. Venetoclax was given at 800 mg adult-equivalent dose when chemotherapy combination was initiated, unless noted below:

- 400 mg adult-equivalent in combination with azacitidine or decitabine
- 400 mg adult-equivalent in combination with imatinib or nilotinib (imatinib and nilotinib are moderate CYP3A inhibitors)
- 400 mg adult-equivalent for patients with TCF3-HLF ALL.

Table 3. Chemotherapy regimens and dosing detail for ALL

Allowed Regimens	Agent	Maximum Dose Allowed[a]
ALL[b]		
Dexamethasone and/or vincristine and/or pegasparaginase[c]	Dexamethasone (or equivalent dose of prednisone)	10 mg/m^2 per day (or equivalent dose of prednisone)
	Vincristine	2 mg/m^2 per day (2 mg max; no more frequently than weekly)
	Pegasparaginase	2,500 IU/m^2/dose per day (Every 2 weeks)
	Cytarabine	1000 mg/m^2 twice per day
	Etoposide	50 mg/m^2 per day (OR 100 mg/m^2 IV daily)
Cytarabine and/or etoposide and/or pegasparaginase[c]	Pegasparaginase	2,500 IU/m^2/dose per day (Every 2 weeks)
ALL with Philadelphia chromosome or with an ABL class targetable fusion		
Tyrosine kinase inhibitor Plus Above regimens for ALL	Imatinib[d] (> 1 year of age)	600 mg/m^2 per day (Continuously)
	Dasatinib	60 mg/m^2 per day (Continuously)
	Nilotinib[d]	100 mg/m^2 twice per day (Continuously)

a. Maximum dosages are listed; Lower doses are allowed, per investigator discretion. Dosing schedule is to be determined by the treating investigator.

b. Patients with lymphoblastic lymphoma may be treated with ALL or NHL regimens.

c. For patients with allergy or intolerance to pegasparaginase, Erwinia asparaginase is acceptable.

d. Imatinib and nilotinib are moderate CYP3A inhibitors. Reduce venetoclax dose by 2-fold (800 mg to 400 mg) when given with imatinib or nilotinib. Refer to Table 7 and Protocol Appendix L for more details.

Table 4. Chemotherapy regimens and dosing detail for AML

Allowed Regimens	Agent	Maximum Dose Allowed[a]
AML		
Cytarabine OR Hypomethylating agents: Azacitidine/Decitabine	Cytarabine	1000 mg/m^2 twice per day
	Azacitidine	75 mg/m^2 per day
	Decitabine	20 mg/m^2 per day

a. Maximum dosages are listed; Lower doses are allowed, per investigator discretion. Dosing schedule is to be determined by the treating investigator.

Table 5. Chemotherapy regimens and dosing detail for NHL

Allowed Regimens	Agent	Maximum Dose Allowed[a]
NHL		
Rituximab and/or dexamethasone and/or vincristine	Rituximab	375 mg/m^2 per day (Weekly)
	Dexamethasone (or equivalent dose of prednisone)	40 mg per day
	Vincristine	1.5 mg/m^2 per day (Weekly; Max 2 mg)

a. Maximum dosages are listed; Lower doses are allowed, per investigator discretion. Dosing schedule is to be determined by the treating investigator.

Table 6. Chemotherapy regimens and dosing details for Neuroblastoma and Solid Tumors

Allowed Regimens	Agent	Maximum Dose Allowed[a]
Neuroblastoma		
Cyclophosphamide + Topotecan[b]	Cyclophosphamide	250 mg/m^2 per day (maximum 5 days every 21 days)
	Topotecan	0.75 mg/m^2 per day (maximum 5 days every 21 days)
Solid Tumors		
Cyclophosphamide and/or Topotecan[b]	Cyclophosphamide	250 mg/m^2 per day (maximum 5 days every 21 days)
	Topotecan	0.75 mg/m^2 per day (maximum 5 days every 21 days)

a. Maximum dosages are listed; Lower doses are allowed, per investigator discretion. Dosing schedule is to be determined by the treating investigator.

b. Myeloid growth factor support must be given beginning 24 – 48 hours following the completion of Cyclophosphamide and/or Topotecan and continued through post-nadir count recovery. Myeloid growth factor must be discontinued at least 24 hours prior to the start of the next course of therapy. Neuroblastoma and solid tumor patients in Part 2 are not required to recover platelet and neutrophil counts prior to the start of their next cycle. It is per principal investigator's discretion if counts are sufficient to start the next cycle and the timing of starting the next cycle. Recommendations for cycle restart can be found in Protocol Section 5.1.2.1 and Table 6 for toxicity management, if needed. Patients should receive full supportive care during study participation, including hematopoietic growth factors, transfusion of blood products, fluid and electrolyte replacement, and antibiotics when appropriate.

Objective(s)

The primary objectives of the study:

- Evaluate the safety of venetoclax monotherapy
- Determine dose limiting toxicities (DLT) and the recommended Phase 2 dose (RPTD) of venetoclax monotherapy
- Assess the pharmacokinetics (PK) of venetoclax monotherapy

The secondary objectives of the study:

- Determine the preliminary efficacy of venetoclax monotherapy
- Evaluate the safety of venetoclax in combination with chemotherapy
- Assess the preliminary efficacy of venetoclax in combination with chemotherapy

The exploratory objectives of the study:

- Evaluate pharmacodynamic and predictive biomarkers
- Assess minimal residual disease (MRD) in the peripheral blood and bone marrow

Outcomes/endpoints

Efficacy

The following efficacy evaluations/endpoints were collected during the study: objective response rate, complete response rate, partial response rate, progression-free survival, overall survival and MRD status. Responses were assessed using established response criteria for each tumor type (amended as relevant for pediatric use).

Safety

The following safety evaluations were performed during the study: adverse event monitoring and laboratory test assessments.

Pharmacokinetics

Plasma concentrations of venetoclax were determined using a validated liquid/liquid extraction followed by high performance liquid chromatography tandem mass spectrometric detection. The lower limit of quantitation for venetoclax was established at 2.00 ng/mL.

PK samples were to be collected during Part 1 and Part 2 until appropriate data for each indication had been collected. An overview of the sampling scheme is shown in Table 7.

Table 7 Overview of planned PK sample collection

Patients with ALL, AML, NHL or Other Hematologic malignancies	
Part 1	W1 Days 1 and 2: 2, 4, 8h W1 Day 3 and W2 Day 8: 0, 2, 4, 6, 8h Additional sampling at Week 3, 4, 8, 12, 24 and every 12 weeks thereafter including final visit
Part 2	Days 1, 2 and 3: 4h W2 Day 8: 0, 2, 4, 6 and 8h Additional sampling at Week 3, 4, 8, 12, 24 and every 12 weeks thereafter including final visit
Patients with Neuroblastoma and Other solid tumors (excluding NHL)	
Part 1 (dose determination)	Day 1: 2, 4 and 8h W1 Day 2 and W2 Day 8: 0, 2, 4, 6 and 8h Additional sampling at Week 3, 4, 8, 12, 24 and every 12 weeks thereafter including final visit
Part 1 (dose descalation/De-escalation, Cohorts S1 & S2 on continuous dosing)	Days 1 and 2: 4h W2 Day 8: 0, 2, 4, 6 and 8h

	Additional sampling at Week 3, 4, 8, 12, 24 and every 12 weeks thereafter including final visit
Part 1 Dose Escalation/De-escalation (Cohorts S-1 & S-2) and in Part 2 (Cohort Expansion) on Intermittent Dosing	Days 1 and 2: 4h W2 Day 8: 0, 2, 4, 6 and 8h Additional sampling at Day 5 of Cycle 2, 3, 4, 8 and every 4th cycle thereafter including final visit

Values for the PK parameters of venetoclax including the maximum observed plasma concentration (Cmax), the time to Cmax (peak time, time to maximum observed concentration [Tmax]), the area under the plasma concentration-time curve (AUC) and apparent clearance (CL/F) were determined using non-compartmental methods as applicable. Dose-normalized Cmax and AUC values were calculated by dividing each of these PK parameters by the adult-equivalent dose.

Sample size

For Part 1 (dose determination), complete data from 10 subjects yielded a two-sided 95% CI within 60% and 140% of the geometric mean PK parameter estimate with 95.4% probability. The calculation assumed a total standard deviation of 0.3403 for the natural logarithm of AUCinf. This value was selected based upon the sum of within-subject and between-subject variances for venetoclax AUCinf from pediatric formulation bioavailability Study M16-069.

The sample size in Part 2 was determined using a Gehan 2-Stage design with beta = 10%, and a target for response rate of 20%. Additional patients may be added if required, particularly in cohorts with disease heterogeneity, to pursue potential signals in different subtypes. The NHL cohort and Cohort 5 may not completely enroll; the NHL cohort may enroll a minimum of 1 patient.

Randomisation and blinding (masking)

This was an open-label Phase 1 study without any active- or placebo control group(s).

Statistical Methods

Efficacy and safety analyses were performed on all subjects who received at least 1 dose of venetoclax, unless otherwise specified.

Efficacy

Analyses were performed for the following five analysis groups: AML, ALL, NHL, Neuroblastoma, Solid Tumors. The Solid Tumor analysis group includes subjects from the exploratory cohort with solid tumors. The Other Tumors analysis group includes all other subjects from the exploratory cohort.

Analysis of ORR (CR + CRi + CRp + PR for ALL and AML, CR + PR for NHL and Solid Tumors, and CR+PR+MR for Neuroblastoma), complete response rate, partial response rate, MRD status, OS, and PFS were performed, and the corresponding 95% CIs were constructed based on binomial distribution for dichotomous endpoints or, respectively, on Kaplan-Meier methodology for time-to-event endpoints.

Safety

The safety of venetoclax was assessed by evaluation of study drug exposure, AEs, SAEs, deaths, and changes in laboratory measures.

Pharmacokinetics

Plasma concentrations of venetoclax and PK parameter values were tabulated for each patient and each dose level. Summary statistics were provided for each dose level and parameter.

Protocol changes

The original protocol, 24 February 2017, (0 subjects) had 5 amendments and 4 administrative changes and 1 country-specific protocol. The amendments and number of subjects enrolled under each amendment were as follows:

- Amendment 1 (13 October 2017, 15 subjects)
- Amendment 2 (23 February 2018, 7 subjects)
- Amendment 3 (19 October 2018, 23 subjects)
- Amendment 4 (25 June 2019, 55 subjects)
- Amendment 5 (09 March 2021, 40 subjects)
- Country Specific (UK 0-01) (05 October 2017, 0 subjects)

The MAH states that the protocol changes described in the amendments and administrative changes did not affect the interpretation of study results.

Statistical changes

There were no changes to the planned analyses after finalization of the SAP.

Results

Participant flow

A total of 140 subjects at 27 sites in Australia, Canada, France, Germany, Netherlands, Switzerland, United Kingdom, and United States were enrolled in Study M13-833.

Enrollment was open until each of the cohorts in Part 2 had been filled, with the exception of the NHL analysis group and the Other Tumors analysis group. Enrollment of subjects ≥18 years of age was halted at times during the study to ensure adequate enrollment of pediatric subjects (<18 years).

In Part 1 (Dose Determination), 22 subjects (10 with AML, 5 with ALL, 0 with NHL, 3 with neuroblastoma, 4 with solid tumors, and 0 with other tumors) were enrolled to ensure sufficient enrollment across all weight ranges and tumor types within each of the following age groups: <2, 2–11, and 12–17 years.

Additionally, 18 subjects with neuroblastoma (N=7) and solid tumors (N=11) were enrolled in Part 1 Dose Escalation/De-escalation. Specifically, Cohort S1, S-1, S-2 each enrolled 6 subjects (2, 5, and 4, respectively, with solid tumors, and 4, 1, and 2, respectively, with neuroblastoma). Cohort S2 did not enroll any subjects based on the Bayesian optimal interval design and incidence of DLTs observed in Cohort S1.

In Part 2, a total of 100 subjects were enrolled into 5 tumor cohorts; ALL (N=26), AML (N=27), NHL (N=2), Neuroblastoma (N=26), and a fifth exploratory analysis group with other tumor types who had evidence of BCL-2 expression and had exhausted curative treatment options. In this exploratory

cohort, N=8 subjects were included in the solid tumors analysis group and N=11 subjects in the other tumors analysis group.

Progressive disease was the leading primary reason for venetoclax discontinuation in most disease analysis groups.

Recruitment

Study initiation date: 8 November 2017 (first subject first visit)

Study completion date: 19 April 2023 (last subject last visit)

Data cut-off date: 14 June 2023

Baseline data

In all subjects with AML (N=37), the majority were female (51.4%) and white (70.6%), with a median (range) age of 6 (0–17) years. Among these subjects, 29.7% had received 3 prior therapies. Most subjects (83.8%) had received >3 platelet transfusions and 75.7% had received >3 red blood cell transfusions. These subjects with AML had a median (minimum [min], maximum [max]) of 1234.0 (8, 1275) days on study. The World Health Organization (WHO) classification at study entry included AML with maturation, AML with minimal differentiation, acute megakaryoblastic leukemia, acute monoblastic/acute monocytic leukemia, and acute myelomonocytic leukemia. The most common WHO classification at study entry was acute monoblastic/acute monocytic leukemia; it was reported in 3 subjects (8.1%).

In all subjects with ALL (N=31), the majority were male (51.6%) and white (83.9%), with a median (range) age of 9 (0–25) years. Among these subjects, 25.8% had received 2 prior therapies. Most subjects (64.5% each) had received >3 platelet transfusions and >3 red blood cell transfusions. These subjects with ALL had a median (min, max) of 64 (20, 175) days on study. The immunophenotypes at study entry included pro-B, common, pre-B, mature-B, pre-T-ALL, pro-T-ALL, T-ALL: cortical, T-ALL: medullary, T-ALL: ETP, T-ALL: near ETP, and other. The most common immunophenotype at study entry was pre-B; it was reported in 6 subjects (19.4%).

In all subjects with NHL (N=2), both were female and white (100% each). One subject was 3 years old, and the other was 21 years old. Among these subjects, one subject had received 3 prior therapies, and one subject had received 6 prior therapies. No subjects had received >3 platelet transfusions or red blood cell transfusions. One subject was on study for 18 days, and the other was on study for 116 days. The Murphy staging at initial diagnosis included Stage I, II, III, and IV. The most common Murphy staging at initial diagnosis was Stage IV; it was reported in both subjects.

In all subjects with Neuroblastoma (N=36), the majority were male (61.1%) and white (78.8%), with a median (range) age of 8 (1–17) years. Among these subjects, 33.3% had received 6 prior therapies. Some subjects (13.9% each) had received >3 platelet transfusions and >3 red blood cell transfusions. These subjects with neuroblastoma had a median (min, max) of 469.0 (36, 1421) days on study. The INSS overall stage at initial diagnosis included Stage I, II, III, IV, and unknown. The most common INSS overall stage at initial diagnosis was Stage IV; it was reported in 21 subjects (58.3%). Bone marrow involvement was reported in 13 subjects (36.1%), with bilateral involvement reported in 10 of these subjects (76.9%). Soft tissue involvement was reported in 23 subjects (63.9%).

In all subjects with Solid Tumors (N=23), the majority were male (60.9%) and white (90.0%), with a median (range) age of 16 (3–24) years. Among these subjects, 43.5% had received 3 prior therapies. Some subjects (17.4% each) had received 1 platelet transfusion and 1 red blood cell transfusion.

These subjects with Solid Tumors had a median (min, max) of 112 (26–1,158) days on study. The overall staging at study entry included Stage 1, 2, 3, 4, and not evaluable. The most common overall staging at study entry was Stage 4; it was reported in 8 subjects (34.8%). The types of primary cancer for Solid Tumors and their overall staging at study entry were as follows: Wilms tumor (Stage 4, M1, N0, NX, T3, TX), gastrointestinal stromal tumor (Stage 4, M1, N0, T0), synovial sarcoma (M1, NX, T2, Stage 4), alveolar rhabdomyosarcoma (not evaluable, MX, NX, TX), biliary tract rhabdomyosarcoma (Stage 3, M0, NX, T2), embryonal rhabdomyosarcoma (Stage 4, M1, NX, TX), Ewing's sarcoma (Not Evaluable, Stage 4, M1, NX, TX, N0, N1, T0), desmoplastic small round cell tumor (staging not provided), NRSTS (BCOR) (M1, N2, T4), and Evans tumor (staging not provided).

In all subjects with Other Tumors (N=11), the majority were male (54.4%), and all were white (100%), with a median (range) age of 10 (5–19) years. Among these subjects, 27.3% had received 2 prior therapies, and 27.3% had received 3 prior therapies. Some subjects (36.4%) had received >3 platelet transfusions, and 27.3% had received >3 red blood cell transfusions. These subjects with Other Tumors had a median (min, max) of 475.5 (128, 613) days on study. The types of primary cancer for Other Tumors included mixed phenotype acute leukemia (B/Myeloid), mixed phenotype acute leukemia (T/Myeloid), myeloid Mpal, secondary ALL with TCF3, HLF fusion, secondary AML, and secondary MDS. The most common primary cancer was secondary MDS; it was reported in 3 subjects (27.3%).

Number analysed

All 140 subjects who received at least 1 dose of study drug were included in the data sets for analysis of safety. Efficacy analysis was performed for all subjects with AML, ALL, NHL, Neuroblastoma or Solid Tumors (N=131). For the 11 subjects with other tumors in the exploratory cohort, which were included in the Other Tumor analysis group, no efficacy analysis was performed due to the many different tumor types enrolled.

The 133 subjects who received study drug and had at least 3 reported PK samples were included in the PK analyses.

Extent of exposure

Extent of exposure (venetoclax)

Table 8. Extent of Exposure - Venetoclax (Full Analysis Set)

Cancer Type:	Total (ALL) (N = 31)	Total (AML) (N = 37)	NHL (N = 2)	NBL (N = 36)	Other Tumors (N = 11)
Duration (days)					
n	31	37	2	36	11
Mean (SD)	40.9 (25.70)	53.4 (61.30)	49.0 (45.25)	123.5 (104.44)	109.7 (68.13)
Median	37.0	35.0	49.0	91.0	93.0
Min, Max	9, 140	7, 282	17, 81	10, 355	22, 269
Relative dose intensity					
n	31	37	2	36	11
Mean (SD)	47.819 (30.8560)	33.860 (24.8263)	54.749 (53.5953)	23.657 (16.7200)	20.775 (8.3884)
Median	41.587	26.071	54.749	18.458	20.056
Min, Max	7.21, 96.95	3.58, 95.94	16.85, 92.65	6.65, 95.00	10.14, 36.30

Cancer Type: Solid Tumors	400 mg Ven cont. + Cyc + Top (Cohort S1) (N = 2)	400 mg Ven int. + Cyc + Top (Cohort S-2) (N = 4)	800 mg Ven int. + Cyc + Top (Cohort S-1) (N = 5)	Part 1 Dose Determination (N = 4)	Part 2 Expansion (N = 8)	Total (N = 23)
Duration (days)						
n	2	4	5	4	8	23
Mean (SD)	234.5 (252.44)	174.5 (130.74)	48.2 (36.94)	363.0 (527.21)	142.3 (164.25)	173.8 (250.50)
Median	234.5	167.0	31.0	142.0	68.0	73.0
Min, Max	56, 413	48, 316	10, 97	30, 1138	10, 507	10, 1138
Relative dose intensity						
n	2	4	5	4	8	23
Mean (SD)	70.438 (11.2299)	32.559 (16.9344)	39.964 (14.2408)	75.295 (23.1818)	44.667 (24.9644)	49.107 (24.3988)
Median	70.438	32.003	37.705	70.210	46.174	50.000
Min, Max	62.50, 78.38	12.55, 53.68	22.44, 56.86	56.01, 104.75	14.62, 95.00	12.55, 104.75

Extent of exposure (chemotherapies)

Among subjects with ALL receiving a Dex/Vin/Peg based regimen (N=20), median exposure to Dex was 28 days, median exposure to Vin was 22 days, and median exposure to Peg (or Erw) was 15 days. For subjects with ALL receiving a cytarabine-based regimen (N=10), median exposure to cytarabine, etoposide, and peg-asparginase was 7, 5, and 8 days, respectively.

Among subjects with AML, median exposure to cytarabine (LD) (N=1), cytarabine (HD) (N=9), decitabine (N=5), and azacitidine (N=19) was 10, 5, 10, and 7 days, respectively.

Among subjects with NHL, median exposure to dexamethasone (N=2), prednisone (N=0), rituximab (N=1), and vincristine (N=2) was 18, NA, 5, and 44 days, respectively.

Among subjects with neuroblastoma (N=36), median exposure to Cyc and Top was 73 and 73 days, respectively.

Among subjects with other tumors (N=11), median exposure to Cyc and Top was 29 days and 173 days, respectively.

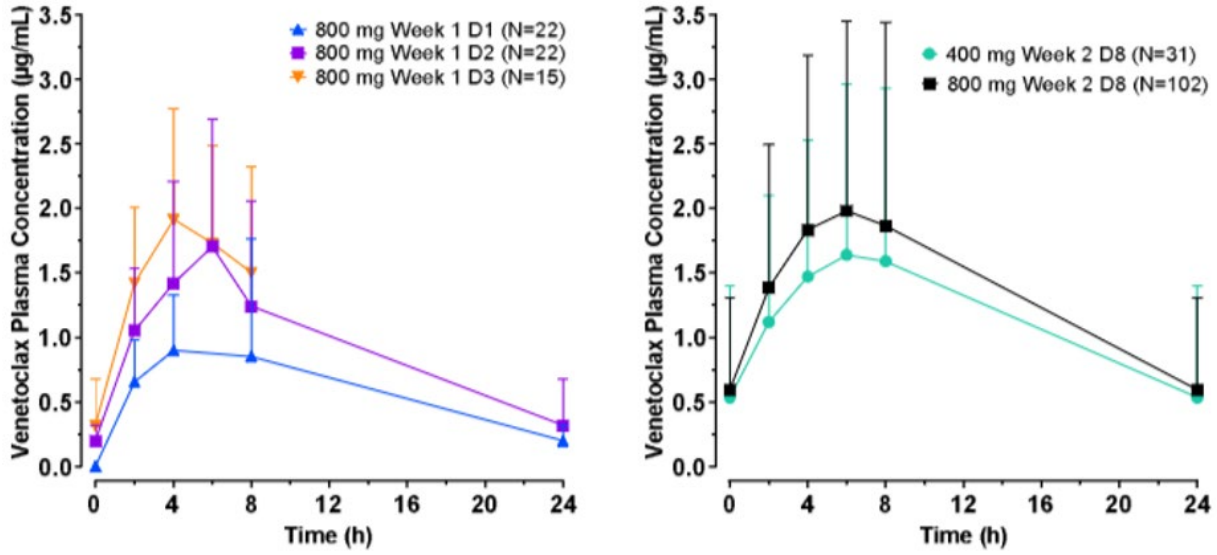
Among subjects with solid tumors (N=11), median exposure to Cyc and Top was 71 and 58 days, respectively.

Assessor's comment

According to the clinical study report, 3 patients in the AML cohort and 1 patient in the ALL cohort received venetoclax monotherapy. Median duration of exposure to venetoclax monotherapy in the AML cohort was 14 days (range 10-21 days); the patient in the ALL cohort received venetoclax monotherapy for 9 days.

Pharmacokinetic results

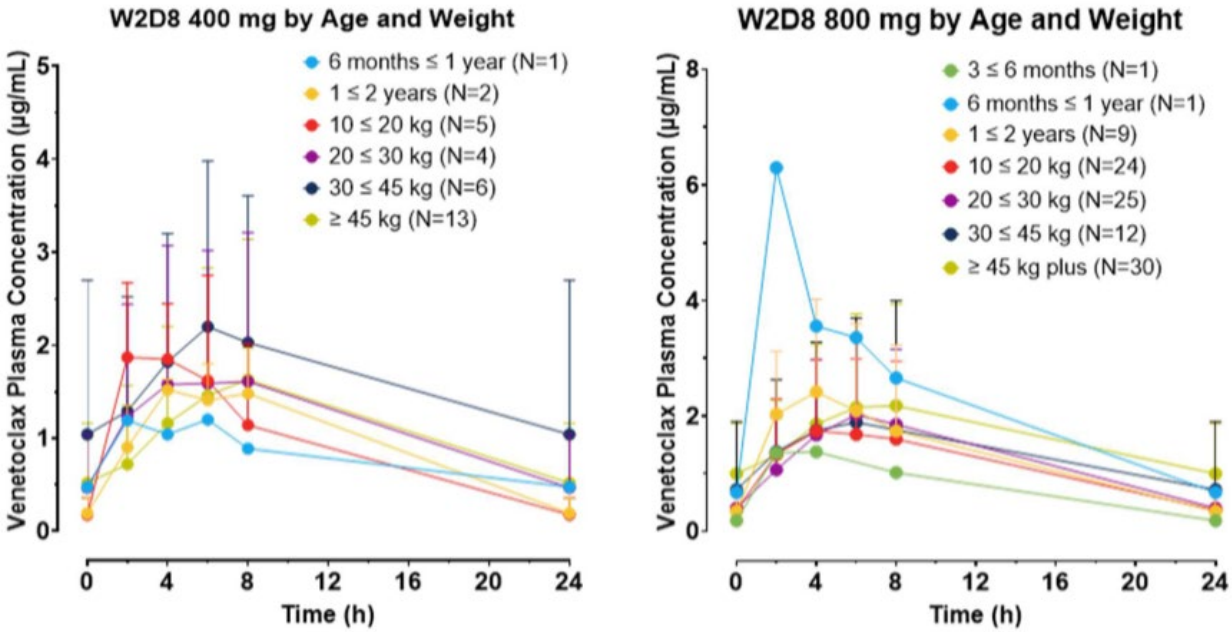
The mean + SD venetoclax plasma concentration-time profiles are presented in Figure 2.



Note: Week 2 Day 8 800 mg dose total number of subjects included was 102, maximum number of subjects at a specific timepoint was 101.

Figure 2 Mean + SD Venetoclax Plasma Concentration-Time Profiles by Visit and equivalent doses

The mean + SD steady state venetoclax plasma concentration-time profiles stratified by age and weight subgroups are presented in Figure 3. A summary of venetoclax PK parameters at steady state is presented in Table 9.



Cross Reference: Data on file at AbbVie

Figure 3 Mean + SD Steady State Venetoclax Plasma Concentration-Time Profiles on Week 2 Day 8 by Age and Weight Subgroups for Both Equivalent Doses

Table 9 Arithmetic Mean±SD (Geometric Mean, %CV) Steady State Pharmacokinetic Parameters of Venetoclax on Week 2 Day 8 by Age and Weight Subgroups for Both Equivalent Doses

	All Subjects	3 ≤ 6 months	6 months ≤ 1 year	1 ≤ 2 Years	10 ≤ 20 kg	20 ≤ 30 kg	30 ≤ 45 kg	≥ 45 kg
Equivalent Dose				**400 mg**				
N	31	--	1	2	5	4	6	13
T_{max} (h)	6.0 (2.3 – 8.1)	--	6.0	6.0 (4.0 – 8.0)	4.0 (2.4 – 6.1)	4.9 (2.3 – 7.9)	6.1 (4.1 – 8.0)	5.8 (3.8 – 8.1)
C_{max} (µg/mL)	1.91±1.38 (1.48, 72.3)	--	1.20	1.44, 1.82	2.25±0.947 (2.09, 42.1)	1.77±1.48 (1.42, 83.7)	2.34±1.78 (1.86, 76.0)	1.71±1.53 (1.18, 89.2)
AUC_8 (µg•h/mL)	10.6±8.13 (8.16, 76.9)	--	8.16	7.64, 11.0	11.9±5.20 (11.1, 43.6)	10.9±10.3 (8.34, 94.5)	13.8±11.7 (10.8, 85.3)	8.84±7.86 (6.23, 89.0)
AUC_{24} (µg•h/mL)	27.5±24.4 (20.4, 88.7)	--	19.0	17.1, 28.0	22.4±13.1 (19.8, 58.3)	27.5±27.5 (20.2, 100)	38.3±36.9 (28.2, 96.4)	26.0±24.3 (17.7, 93.6)
Equivalent Dose				**800 mg**				
N	102	1	1	9	24	25	12	30
T_{max} (h)	4.4 (0.0 – 8.6)	4.0	2.2	4.1 (1.9 – 6.1)	4.0 (0.0 – 8.5)	6.0 (0.0 – 8.3)	5.2 (2.1 – 8.6)	6.1 (2.0 – 8.3)
C_{max} (µg/mL)	2.28±1.66 (1.77, 72.8)	1.38	6.30	2.49±1.57 (1.93, 63.1)	2.01±1.40 (1.58, 69.8)	2.14±1.38 (1.78, 64.3)	2.15±2.06 (1.54, 95.8)	2.50±1.86 (1.94, 74.3)
AUC_8 (µg•h/mL)	12.7±9.17 (9.87, 72.4)[a]	9.09	29.6	15.0±9.66 (11.4, 64.5)	11.4±7.89 (9.04, 69.3)	11.6±8.16 (9.51, 70.2)	12.3±12.0 (8.80, 97.1)	13.6±9.65 (10.6, 71.1)[c]
AUC_{24} (µg•h/mL)	31.9±25.4 (24.2, 79.7)[b]	18.7	56.2	31.7±22.8 (22.9, 72.0)	26.4±19.6 (20.1, 74.1)	28.8±19.0 (24.2, 65.8)	32.7±37.4 (21.2, 114)	38.5±29.7 (29.9, 77.0)[d]

a. N=101
b. N=100
c. N=29
d. N=28
Note: Tmax expressed as median (minimum - maximum).
Week 2 Day 8 400 mg 1 ⩽ 2 Years individual values are reported.

MAH conclusion regarding pharmacokinetics: In pediatric subjects with relapsed/refractory malignancies, the use of age and weight-based dosing scheme yielded comparable venetoclax plasma exposures across different age and weight subgroups.

Efficacy results

Per the clinical protocol, disease response was assessed by the investigator using established response criteria for each tumor type. For this study, all subjects who received at least 1 dose of study drug were included in the efficacy analyses with the exception of subjects in the Other Tumors analysis group.

Table 10. Summary of efficacy results in subjects with AML, ALL, NHL, Neuroblastoma, and Solid Tumors from Study M13-833

Endpoint	Result
AML (N = 37)	
Objective response rate,[a] n (%)	9 (24.3)
Complete response rate,[b] n (%)	6 (16.2)
Partial response rate, n (%)	3 (8.1)
Median duration of response, days (95% CI)	78.0 (15.0, 240.0)
Median time to best response, days (min, max)	36.0 (21, 85)
Median overall survival, days (95% CI)	110 (76, 216)
Median progression-free survival, days (95% CI)	42 (31, 76)
ALL (N = 31)	
Objective response rate,[a] n (%)	13 (41.9)
Complete response rate,[b] n (%)	13 (41.9)
Partial response rate, n (%)	0
Median duration of response, days (95% CI)	311 (84, 432)
Median time to best response, days (min, max)	23 (21, 50)
Median overall survival, days (95% CI)	118 (75, 290)
Median progression-free survival, days (95% CI)	28 (22, 95)
NHL (N = 2)	
Objective remission rate,[c] n (%)	1 (50.0)
Complete remission rate, n (%)	0
Partial remission rate, n (%)	1 (50.0)
Median duration of response, days (95% CI)	NE
Median overall survival, days (95% CI)	NE
Median progression-free survival, days (95% CI)	NE
Neuroblastoma (N = 36)	
Objective response rate,[d] n (%)	11 (30.6)
Complete response rate, n (%)	8 (22.2)
Partial response rate, n (%)	3 (8.3)
Median duration of response, days (95% CI)	283 (120, NE)
Median overall survival, days (95% CI)	431 (195, 721)
Median progression-free survival, days (95% CI)	114 (58, 224)
Solid Tumors (N = 23)	
Objective response rate,[c] n (%)	5 (21.7)
Complete response rate, n (%)	1 (4.3)
Partial response rate, n (%)	4 (17.4)
Median duration of response, days (95% CI)	336.5 (94.0, NE)
Median overall survival, days (95% CI)	180 (107, 714)
Median progression-free survival, days (95% CI)	88 (49, 245)

CI = confidence interval; CR = complete response; CRi = complete response incomplete recovery; CRp = complete response without platelet recovery; max = maximum; min = minimum; MR = minor response; NE = not estimable; PR = partial response.

a. CR + CRi + CRp + PR.

b. CR + CRi + CRp.

c. CR + PR.

d. CR + PR + MR.

Safety results

All subjects who received at least 1 dose of venetoclax were included in the safety analyses.

AML

In subjects with AML (N=37), the most common (i.e., top two frequencies) treatment-emergent adverse events (TEAEs) were vomiting (64.9%) and febrile neutropenia (56.8%). The most common Grade 3 or 4 TEAEs were febrile neutropenia (56.8%) and hypokalemia (37.8%).

A total of 31 subjects (83.8%) died including 3 deaths due to adverse events (AEs); these included 1 event each of hypoxia, pulmonary hemorrhage, and respiratory failure.

Twenty-eight subjects (75.7%) experienced a serious adverse event (SAE). These included febrile neutropenia (48.6%), and bacteremia, cellulitis, and sepsis (5.4% each). All other AEs were reported in 1 subject each.

Seven subjects (18.9%) had AEs leading to discontinuation of venetoclax. All AEs leading to discontinuation of Venetoclax were reported in 1 subject (2.7%) each. These events included neutropenia, ileus, pancreatitis, fungal infection, pneumonia, malignant neoplasm progression, and respiratory failure.

ALL

In subjects with ALL (N=31), the most common TEAEs were alanine aminotransferase increased and febrile neutropenia (54.8% each), and hypokalemia (51.6%). The most common Grade 3 or 4 TEAEs were febrile neutropenia (54.8%) and hypokalemia (38.7%).

A total of 23 subjects (74.2%) died including 6 deaths due to AEs; these included 2 events each of multiple organ dysfunction syndrome and pneumonia, and 1 event each of malignant neoplasm progression and respiratory failure.

Twenty-four subjects (77.4%) experienced an SAE. These included febrile neutropenia (41.9%), sepsis (16.1%), pneumonia (9.7%), and abdominal pain, multiple organ dysfunction syndrome, pneumonia fungal, malignant neoplasm progression, neurotoxicity, seizure, respiratory failure, and hypotension (6.5% each). All other AEs were reported in 1 subject each.

Six subjects (19.4%) had AEs leading to discontinuation of venetoclax. All AEs leading to discontinuation of Venetoclax were reported in 1 subject (3.2%) each. These events included disease progression, multiple organ dysfunction syndrome, hepatosplenomegaly, atypical mycobacterial pneumonia, pneumonia, sepsis, soft tissue infection, malignant neoplasm progression, and respiratory failure.

NHL

In subjects with NHL (N=2), TEAEs reported in 1 subject included anemia, vomiting, febrile neutropenia, nausea, neutrophil count decreased, pyrexia, constipation, aspartate aminotransferase increased, alanine aminotransferase increased, pruritis, stomatitis, leukopenia, hypertension, sepsis, gamma-glutamyl transferase increased, dyspnea, face edema, insomnia, blood lactate dehydrogenase increased, streptococcal infection, anal inflammation, blood uric acid increased, depressed mood, enterococcal infection, generalized edema, hepatomegaly, peripheral sensory neuropathy, and staphylococcal infection. Grade 3 or 4 TEAEs reported in 1 subject included anemia, febrile neutropenia, leukopenia, stomatitis, sepsis, streptococcal infection, alanine aminotransferase increased, gamma-glutamyl transferase increased, neutrophil count decreased, and hypertension. One subject (50.0%) died; the death was not due to an AE. One subject (50.0%) experienced an SAE (sepsis). No subjects had AEs leading to discontinuation of venetoclax.

Neuroblastoma

In subjects with neuroblastoma (N=36), the most common TEAEs were anemia and febrile neutropenia (77.8% each) and vomiting (75.0%). The most common Grade 3 or 4 TEAEs were anemia and febrile neutropenia (77.8% each), and neutrophil count decreased (52.8%).

A total of 20 subjects (55.6%) died, including 1 death due to AEs; these included 1 event each of multiple organ dysfunction and pneumonia fungal.

Thirty-four subjects (94.4%) experienced an SAE. These included febrile neutropenia (69.4%), anemia and hypotension (11.1% each), pyrexia, sepsis, and platelet count decreased (8.3% each), and rhinovirus infection and neutrophil count decreased (5.6%). All other AEs were reported in 1 subject each.

Six subjects (16.7%) had AEs leading to discontinuation of venetoclax. All AEs leading to discontinuation of Venetoclax except febrile neutropenia (2 subjects, 5.6%) were reported in 1 subject (2.8%) each. These events included neutropenia, thrombocytopenia, diarrhea, pneumonia fungal, platelet count decreased, and hypotension.

Solid tumours

In subjects with Solid Tumors (N=23), the most common TEAEs were anemia (73.9%) and febrile neutropenia and nausea (60.9% each). The most common Grade 3 or 4 TEAEs were anemia (69.6%) and febrile neutropenia (60.9%).

A total of 16 subjects (69.6%) died, including 2 deaths due to AEs; these included 1 event each of cardiac failure, pericardial effusion, multiple organ dysfunction syndrome, Escherichia sepsis, and hypotension.

Eighteen subjects (78.3%) experienced an SAE. These included febrile neutropenia (56.5%), and abdominal pain, vomiting, back pain, and cystitis hemorrhagic (8.7% each). All other AEs were reported in 1 subject each.

Two subjects (8.7%) had AEs leading to discontinuation of venetoclax. All AEs leading to discontinuation of Venetoclax were reported in 1 subject (4.3%) each. These events included febrile neutropenia, vomiting, and muscular weakness.

Other tumours

In subjects with Other Tumors (N=11), the most common TEAEs were anemia, white blood cell count decreased, and lymphocyte count decreased (90.9% each), vomiting and nausea (81.8% each). The most common Grade 3 or 4 TEAEs were anemia, lymphocyte count decreased, and white blood cell count decreased (90.9% each) and neutrophil count decreased (72.7%).

A total of 7 subjects (63.6%) died. These deaths were not due to AEs.

Five subjects (45.5%) experienced an SAE. These included febrile neutropenia (27.3%), and bacteremia and vascular device infection (18.2% each). All other AEs were reported in 1 subject each.

Two subjects (18.2%) had AEs leading to discontinuation of venetoclax. All AEs leading to discontinuation of Venetoclax were reported in 1 subject (9.1%) each. These events included platelet count decreased and white blood cell count decreased.

Deaths

In all 140 subjects, a total of 98 deaths were reported in this study as of 19 April 2023, the LSLV date for this final report. The primary cause of death among almost all subjects was reported as "Disease Progression" per the investigator's assessment. Among all analysis groups, TEAEs leading to death were reported in 12 subjects overall and include multiple organ dysfunction syndrome, pneumonia,

malignant neoplasm progression, respiratory failure, hypoxia, pulmonary hemorrhage, pneumonia fungal, cardiac failure, pericardial effusion, Escherichia sepsis, and hypotension. Treatment-emergent AEs leading to death considered possibly related to chemotherapy agents were reported in 1 subject; these events were pneumonia fungal and multiple organ dysfunction syndrome. Among subjects with neuroblastoma, 1 subject who had a Grade 5 fungal pneumonia that caused multiorgan failure died; this death was considered possibly related to venetoclax. Among subjects with ALL, 1 subject had a Grade 5 pneumonia assessed as possibly related to venetoclax; however, after being originally reported as a death from an AE, the cause of death was re-assessed by the investigator as related to disease progression.

2.3.3. Discussion on clinical aspects

The MAH has submitted the final results for study M13-833 in accordance with the Article 46 of Regulation (EC) No. 1901/2006.

Study M13-833 was an open-label, global, Phase 1, dose determination (consisting of both a dose determination and dose escalation/de-escalation component) and cohort expansion study in paediatric and young adult subjects with relapsed or refractory malignancies.

Treatment with venetoclax was ramped-up to the target dose over 2 (for solid tumours) or 3 days (for AML, ALL and NHL); on Day 3 (for solid tumours) or Day 4 (for AML, ALL and NHL) chemotherapy was added with different chemotherapy regimens depending on the tumour diagnosis.

A total of 140 patients were enrolled and analysed in the following tumour cohorts: AML, ALL, NHL, neuroblastoma, solid tumours (primary tumours expressing BCL-2) and other tumours (other haematological malignancies). Of these malignancies, only AML is an approved indication in adults.

Patient disposition and age across the cohorts was as follows: AML (N=37), median age of 6 years (range 0-17 years); ALL (N=31), median age of 9 years (range 0–25 years); NHL (N=2), 3 years and 21 years, respectively; neuroblastoma (N=36), with a median age of 8 years (range 1-17 years); solid tumours (N=23), median age of 16 years (range 3-24 years); other tumours (N=11), median age of 10 years (range 5-19 years).

Pharmacokinetics

A reasonable PK sampling schedule has been used to characterise the paediatric PK profile in Study M13-833. The PK parameters included Cmax, tmax and AUC which is considered reasonable parameters to derive using non-compartmental analysis given the PK sampling design. The PK sampling was most intense at Week 2 Day 8 which is considered representative of steady-state and this time-point is considered relevant. Multiple PK samples were also collected during in Part 1 on Days 1-3 of treatment which was also reported (Figure 2). Additional samples were also to be collected using a sparse PK sampling design at later visits during treatment (Table 7).

For Week 2 Day 8, the PK results were stratified based on body weight and age (Table 9, Figure 3). Overall, the exposure seems to be comparable across the different age- and weight groups. However, a limitation is that the PK exposures in Study M13-833 were not compared with the corresponding adult exposure following 800 and 400 mg, i.e. it was not possible to assess whether the applied paediatric doses (Table 2) give rise to exposures which are equivalent to adult exposures.

As an update of the SmPC based on the results from Study M13-833 will be relevant (see below), information on the PK exposure in paediatric patients compared to adults should be included in SmPC section 5.2.

Efficacy

The ORR and CR rates in the AML cohort were 24.3% and 16.2%, respectively, and in the ALL cohort 41.9% (all CR). The estimated median DOR was 78 days (95% CI: 15, 240) for AML and 311 days (95% CI: 84, 432) for ALL. ORR and CR rates in the neuroblastoma cohort were 30.6% and 22.2%, respectively, with an estimated median DOR of 283 days (95% CI: 120, NE).

Although assessment of efficacy is hampered by the lack of a control arm and the small number of patients included in each cohort, the results in terms of response rate indicate anti-tumour activity in patients with AML, ALL or neuroblastoma treated with venetoclax in combination with chemotherapy.

For the other tumours cohort, no analysis of efficacy was undertaken by the MAH due to the many different tumour types enrolled; this is acknowledged. Given the low number of patients included in the NHL and solid tumours cohort, as well as the diversity of tumour types included in the latter cohort, and the lack of a control arm, no conclusions can be drawn regarding efficacy for those tumour cohorts.

Safety

The median duration of exposure to venetoclax ranged from 35 days in the AML cohort to 93 days in the other tumours cohort. Three patients in the AML cohort and 1 patient in the ALL cohort received venetoclax monotherapy; duration of exposure for these 4 patients ranged from 9 to 21 days.

Across all tumour cohorts, the most common TEAEs concerned febrile neutropenia, anaemia and gastrointestinal AEs (vomiting or nausea). Common grade 3 or 4 TEAEs were febrile neutropenia and hypokalaemia. Across all tumour cohorts, the incidence of SAEs ranged from 45.5% in the other tumours cohort to 94.4% in the neuroblastoma cohort. Across all tumour cohorts, 12 TEAEs leading to death were reported. Of these, TEAEs leading to death (fungal pneumonia and multiple organ dysfunction) assessed by the investigator as possibly related to venetoclax were reported in 1 patient in the neuroblastoma cohort.

The reported TEAEs for the 4 patients receiving venetoclax monotherapy were consistent with the known safety profile for venetoclax. However, given the small number of patients and the short treatment duration, no firm conclusions can be drawn. The overall safety profile reported for venetoclax in combination with chemotherapy seems to be consistent with the established safety profile for venetoclax; no new safety signals could be identified. However, the assessment of safety is hampered by the lack of a control arm, the various chemotherapy regimens and the diversity of the underlying tumour types.

Product information

The SmPC for Venclyxto states the following regarding paediatric use:

Section 4.2

Paediatric population

The safety and efficacy of venetoclax in children aged less than 18 years have not been established. No data are available.

Section 5.1

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Venclyxto in all subsets of the paediatric population in CLL (see section 4.2 for information on paediatric use).

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

The MAH has not proposed an update of the product information as part of this procedure. However, according to the paediatric regulation ((EC) No 1901/2006), results from paediatric studies, even when there is lack of activity, should be included in the SmPC to provide guidance to prescribers. Furthermore, the current text on deferral of studies with Venclyxto in one or more subsets of the paediatric population for the treatment of AML should be amended to reflect finalisation of study M13-833. Section 4.2 should be amended accordingly.

3. Rapporteur's overall conclusion and recommendation

No firm conclusions can be drawn regarding efficacy and safety in paediatric patients with AML, ALL, NHL, neuroblastoma, solid tumours or other tumours treated with venetoclax in combination with chemotherapy.

Presentation of PK data is considered acceptable in the context of this p46 procedure.

The SmPC should be updated with a brief description of the results of study M13-833 (section 5.1); the current texts on deferral of paediatric studies (section 5.1) and lack of data (section 4.2) should be updated to reflect finalisation of the study, as detailed below. In addition, a brief description of the PK exposure in paediatric patients of study M13-833, in relation to adult PK exposures should be included in SmPC section 5.2.

☒ **Fulfilled:**
In view of the available data regarding efficacy in paediatric patients the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and ***no later than 60 days after the receipt*** of these conclusions.

- Section 5.1 of the SmPC should be updated with a brief description of the results of study M13-833 (number of patients, the diagnoses included and efficacy data in terms of response rates).
- The current deferral information in section 5.1 should be updated to reflect finalisation of the study.
- In section 4.2 the information under the heading paediatric population should be updated by replacing the text 'No data are available' with the statement as per the SmPC guideline (Currently available data are described in section <4.8><5.1><5.2> but no recommendation on a posology can be made).
- Section 5.2 of the SmPC should be updated with a brief description of PK exposure in paediatric patients of study M13-833, in relation to adult PK exposures.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non-clinical studies

Product Name: Venclyxto Active substance: Venetoclax

Study title	Study number	Date of completion	Date of submission of final study report
Define juvenile toxicity study to determine the potential effects of venetoclax on development (Study 2)	Not available	October 2016	December 2018

Clinical studies

Product Name: Venclyxto Active substance: Venetoclax

Study title	Study number	Date of completion	Date of submission of final study report
A Phase 1 Study of the Safety and Pharmacokinetics of venetoclax in Pediatric and Young Adult Patients with Relapsed or Refractory Malignancies (Study 3)	M13-833	By December 2023	By October 2023
Evaluation of efficacy of venetoclax in paediatric patients from birth to less than 18 years of age (and young adults) with select paediatric solid or haematologic tumour type prioritized based on anti-tumour activity in study M13-833 (Study 4)	Not available	By October 2026	Not available
A randomized, open-label, controlled, global study, to evaluate the efficacy of venetoclax (VEN) in combination with fludarabine and high dose cytarabine (FLA) and gemtuzumab ozogamicin (GO) (FLA+GO+VEN) compared with FLA+GO alone in children with relapse acute myeloid leukemia (AML) without FLT3/ITD mutation (Study 5)	B19-061	By December 2029	Not available