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Committee for Medicinal Products for Human Use (CHMP)

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

NINLARO

Ixazomib

Procedure no: EMEA/H/C/003844/P46/014

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	26/06/2024	24/06/2024	☐
☐	CHMP Rapporteur Assessment Report	29/07/2024	30/07/2024	☐
☐	CHMP members comments	12/08/2024	N/A	☐
☐	Updated CHMP Rapporteur Assessment Report	16/08/2024	N/A	☐
☒	CHMP adoption of conclusions:	22/08/2024	22/08/2024	☐

[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

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1. Introduction

On June 11, 2024, the MAH submitted a completed paediatric study T2017-002 for Ninlaro (ixazomib), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The CSR submitted in the context of this application covers the phase 2 portion of the study, corresponding to Study 4 in the Ninlaro PIP. A short critical expert overview has been provided.

The single-arm phase 1 of this study (PIP Study 2) has been submitted to EMA on 15 Nov 2021 (see procedure EMEA/H/C/003844/P46/012).

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study T2017-002 is part of a clinical development program (Paediatric Investigation Plan EMEA-001410-PIP02-17). The variation application consisting of the full relevant data package (i.e containing several studies) is expected to be submitted by December 2031. A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

In the Therapeutic Advances in Childhood Leukemia & Lymphoma (TACL) consortium Study T2017-002, ixazomib was given on Days 1, 4, 8, and 11 of each cycle. The formulation of ixazomib was either a liquid formulation (administered via oral syringe or nasogastric feeding tube) or an oral capsule.

The liquid formulation consisted of ixazomib (as a lyophilized drug product) diluted with flavouring agents.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for the Phase 2 portion of clinical study T2017-002 (PIP study 4) in children with relapsed/refractory acute lymphoblastic leukemia/lymphoma (ALL). Final results for the Phase 1 part of study T2017-002 (PIP study 2) have already been submitted (see procedure EMEA/H/C/003844/P46/012).

Acute lymphoblastic leukaemia/ lymphoblastic lymphoma (ALL)

ALL is a rare form of leukemia that affects children more than adults, boys and men more frequently than girls and women. ALL accounts for, approximately, 1/3 of all paediatric malignancies, being the most common form of haematologic neoplasm in children (see e.g. Ward E et al, CA Cancer J Clin. 2014). The incidence of ALL in children is 40 cases per million among industrialized Western European countries and up to 35 cases per million in Eastern European countries (see e.g. Parkin DM et al, Int J Cancer 1988).

The incidence peak is between 0 and 5 years in Europe and the United States. In Europe, ALL accounts for 80% of leukemias in children aged <15 years. A study from the Nordic group showed that the

incidence of ALL among children has been stable in the time period 1983-2002 (i.e. 3.3 cases per 100,000 in children <15 years old, see e.g. Svendsen AL et al, J Pediatr. 2007).

Despite ongoing progress in improving event-free survival (EFS) for paediatric patients with ALL, nearly 15 to 20% are still expected to relapse, and the outcome for relapsed patients is unsatisfactory, with only approximately one-half of patients achieving long-term survival. The therapy for relapsed or refractory ALL is risk-adapted, with factors like lymphoblast-lineage, presence of genetic markers (eg. T9:22), duration of first remission and type of relapse (e.g. medullary vs. isolated extramedullary relapse) guiding treatment choice. The aim of salvage therapy is, anyway, to induce a new CR (CR2), and most re-induction regimens are based on similar four-drug backbones, including e.g. corticosteroids, vincristine, daunorubicin or mitoxantrone, and asparaginase (although different non-cross resistant chemotherapy platforms might be preferred in children with early bone marrow relapse). The rate of CR2 with risk-based re-induction regimens is comprised between 60 and 100%, depending on risk group (see eg. Parker C et al, Lancet Haematol. 2019; Raetz EA et al, JCO 2008; Tallen G et al, JCO 2010). A recent study evaluated the addition of bortezomib (a first-in-class proteasome inhibitor) to standard re-induction therapy in relapsed/refractory paediatric ALL, resulting in CR2 rates reaching 70% (see e.g. Hortin TM et al, Br J Haematol 2019).

Even when CR2 is achieved, further consolidation with allogeneic haematopoietic stem cell transplant (allo-HSCT) is still needed to allow for long term disease control, the only exceptions being patients with late isolated extramedullary site relapse, late bone marrow relapse with MRD-negativity at the end of re-induction, or children deemed unfit for transplantation, who might instead benefit from further consolidation/maintenance chemotherapy.

For children in second or later relapse, or with their disease relapsing post-alloHSCT, anti-CD19 immunotherapies including e.g. blinatumomab and tisagenlecleucel (a CAR T cell ATMP targeting CD19) are approved and can result in significant CR rates, although their potential to allow for long-term disease control needs to be further characterised.

About the product

Ixazomib is a proteasome inhibitor that has been granted marketing authorization (MA) in the European Union (EU) to treat adult patients with multiple myeloma who have received at least 1 prior therapy.

Proteasome inhibitors (PIs) are small molecules that target the 20S proteasome. The ubiquitin-proteasome system is the major regulatory system through which protein homeostasis occurs and represents the primary mechanism by which cells degrade proteins, including those involved in growth control, cell cycle regulation, and apoptosis. The 26S proteasome is composed of a catalytic proteolytic core (20S) and 2 regulatory subunits (19S).

Studies showed that bortezomib, the first-in-class PI, has the ability to potentiate the antitumor effects of standard cytotoxic chemotherapy in childhood leukaemia (see e.g. Horton et al. 2006; Lee et al. 2011) and that bortezomib is active in the treatment of paediatric patients with relapsed ALL/LLy (see e.g. Bertaina et al. 2017; Messinger et al. 2010; Messinger et al. 2012).

Like bortezomib, ixazomib (the only PI with an oral formulation) selectively inhibits the β5 site of the 20S proteasome and demonstrated synergistic activity with dexamethasone and doxorubicin in nonclinical studies (see e.g. Chauhan et al, Clin Cancer Res 2011). In nonclinical studies, ixazomib has also shown increased potency and superior activity over bortezomib, potentially because of its shorter proteasome dissociation half-life leading to a higher tumor-to-blood ratio of proteasome inhibition (see e.g. Dick and Fleming 2010; Kupperman et al. 2010; Lee et al. 2011). Ixazomib has demonstrated antitumor effect in a paediatric T-cell ALL xenograft model (see Ravi et al. 2016), and there have been

3 investigator-initiated studies of ixazomib in adult patients with ALL. Two phase 1 studies demonstrated that the maximum tolerated doses (MTDs) of ixazomib are schedule- and formulation-dependent [intravenous, 1.75 mg/m^2 (Smith et al. 2015); oral, 2.0 mg/m^2 (Richardson et al. 2014)]. A phase 1/2 study of oral ixazomib used in combination with lenalidomide and dexamethasone demonstrated a recommended phase 2 dose (RP2D) of 2.2 mg/m^2 (Kumar et al. 2014).

The encouraging data of bortezomib in paediatric ALL and the results of xenograft-model studies of proteasome inhibition by ixazomib led TACL to conduct a phase 1/2 study using ixazomib as part of combination chemotherapy in children with relapsed and/or refractory ALL. The Marketing Authorisation Holder (MAH), however, also highlighted that, since study T2017-002 was designed, the treatment landscape for children with relapsed and/or refractory ALL has evolved to primarily use antibody drug conjugates, T-cell engaging bispecific antibodies, and cellular therapies (Hoelzer et al. 2024).

2.3.2. Clinical study

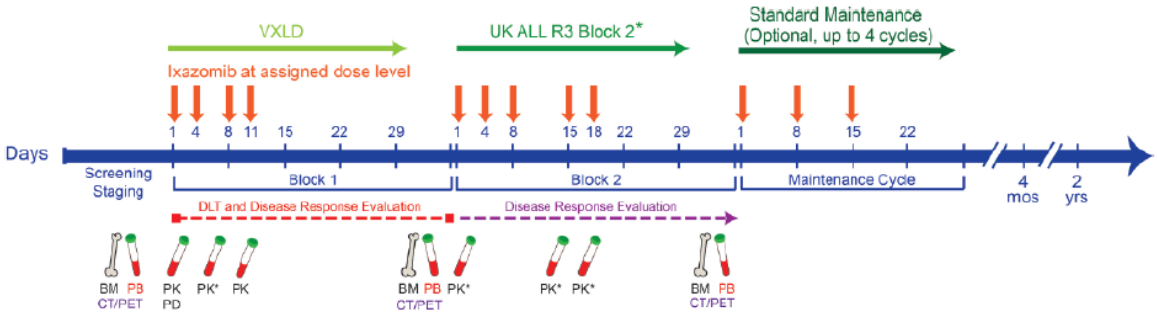
Study T2017-002 Phase 2 - "A TACL Phase 1/2 Study of PO Ixazomib in Combination with Chemotherapy for Childhood Relapsed or Refractory Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma (IND #140730)"

Description

Study T2017-002, conducted by the *Therapeutic Advances in Childhood Leukemia and Lymphoma* (TACL) consortium in the United States, was a Phase 2 open label, non-randomized, dose expansion study to estimate the efficacy of the per os (PO) formulation of ixazomib in combination with chemotherapy in children with relapsed acute lymphoblastic leukemia/lymphoma (ALL).

The study design is summarised in Figure below:

Figure 1.a Study T2017-002 Design



The ixazomib dose level in all patients in phase 2 of the study was the RP2D: 2 mg/m^2/dose.
* UK ALL R3 Block 2 (consolidation) therapy was not required for patients who achieved complete remission; complete remission, minimal residual disease negative; or complete response with incomplete count recovery after Block 1 therapy; these patients had the option of receiving Block 2 therapy, moving directly to receiving maintenance therapy with ixazomib for up to 4 cycles, or going off protocol therapy. Any patients who had partial response or stable disease after Block 1 therapy were able to continue on to Block 2 therapy.
"PK*" indicates PK samples that were collected in phase 2 only (ie, Block 1 Day 8 and Block 2 Days 1, 15, 18).
ALL: acute lymphoblastic leukaemia; BM: bone marrow; CT: computed tomography; PB: peripheral blood; PD: pharmacodynamics; PET: positron emission tomography; PK: pharmacokinetics; UK: United Kingdom; VXLD: vincristine, dexamethasone, asparaginase, doxorubicin.

Methods

Study participants

The study population consisted of paediatric patients 21 years of age or younger, with documented relapsed or refractory ALL/LLy with or without extramedullary disease (including CNS 2 and CNS3). Enrolment onto this study was initially restricted to only patients under 18 years of age until 9 such patients were enrolled.

Key inclusion criteria

- Patients with ALL must have ≥ 5% blasts by morphology.
- Patients with LLy must have measurable disease documented by clinical, radiologic or histologic criteria.
- Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study (at least 7 days must have occurred since the last dose of a biologic agent).

Key exclusion criteria

- Patients with mixed phenotype ALL or mature B (Burkitt-like) leukemia
- Patients with isolated CNS or testicular disease
- Patients with a known allergy or intolerance to any of the drugs used in the study – except for PEG-asparaginase for which erwinia asparaginase may be substituted
- Patients with a systemic fungal, bacterial, viral or other infection that is exhibiting ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics or other treatment. The patient needs to be off pressors and have negative blood cultures for 48 hours

Treatments

Ixazomib: Days: 1, 4, 8, and 11. At least 72 hours must have elapsed between doses. The dose of ixazomib was assigned to the patient at the RP2D (2 mg/m^2/dose PO for patients aged ≥1 year; 0.07 mg/kg/day PO for patients aged <1 year). The dose the patient was assigned and received during treatment block 1 remained the same if the patient continued to treatment block 2 or optional maintenance therapy. Oral ixazomib was tested in this study in 2 formulations: the oral formulation (hard capsules) and the ixazomib powder for solution for injection reconstituted for oral administration (via oral syringe) or gastric administration (via nasogastric tube).

Vincristine: IV push over 1 minute or infusion via minibag as per institutional policy on Days 1, 8, 15 and 22. Dose: ≥ 1 year: 1.5 mg/m^2/dose (maximum dose 2mg); ≥ 6 months and < 1 year: 1.2 mg/m^2/dose; < 6 months: 1 mg/m^2/dose.

Dexamethasone: PO or IV on Days 1-14. Dose: ≥ 1 year: 10mg/m^2/day, divided BID (i.e., 5mg/m^2/dose, BID); ≥ 6 months and < 1 year: 8mg/m^2/day, divided BID (i.e., 4 mg/m^2/dose, BID); < 6 months: 7 mg/m^2/day, divided BID (i.e., 3.5 mg/m^2/dose, BID).

Pegaspargase or Calaspargase: IV over 1-2 hours or IM (patients are to receive either Pegaspargase OR Calaspargase) on Days 2, 15 (Calaspargase only on Day 2). Dose ≥ 1 year: 2.500 International units

(IU)/m^2/dose; ≥ 6 months and < 1 year: 2.000 IU/m^2/dose; < 6 months: 1.750 IU/m^2/dose. Calaspargase: IV over 1-2 hours 2. Patients with allergic reaction to Calaspargase OR Pegaspargase can be given Erwinase IM/IV or Rylaze IM/IV on Mon/Wed/Fri (or every other day per institutional standard) x 6 doses for each dose of Pegaspargase replacement.

Doxorubicin: IV over 15 minutes on Day 1. Dose ≥ 1 year: 60mg/m^2/dose; ≥ 6 months and < 1 year: 48 mg/m^2/dose; < 6 months: 42mg/m^2/dose

Intrathecal (IT) Methotrexate (MTX): for CNS 1/2 patients only on days 1, 15, and 29. Dose according to age.

Triple IT Chemotherapy (including MTX, HC and ARAC): for CNS 3 patients only on Days 8, 15, 22, and 29. Dose according to age.

Objective(s)

The Phase 2 primary objective and related endpoint of the study is as follows:

Primary Objective	Endpoint for primary objective
Determine the efficacy of PO ixazomib administered in conjunction with block (cycle) 1 re-induction chemotherapy in children with relapsed/refractory ALL or lymphoblastic lymphoma (LLy)	Response (CR+ CR MRD-, and CR + CR MRD- + CRi) after block 1 chemotherapy

Outcomes/endpoints

Assessment of efficacy

All evaluations of disease were to be performed during the eligibility screening and at the end of each treatment cycle.

A bone marrow aspiration (biopsy is optional) and CT and PET (lymphoma patients only) to assess remission status were performed not earlier than study Day 29. The bone marrow evaluation could be delayed no later than day 36 (± 1 day) if ANC < 500/µL and platelet < 20,000/µL, platelet infusion independent, on day 29.

If the marrow was hypoplastic and/or there was little or no evidence of normal hematopoiesis, a repeated marrow should be performed after every 7-21 days (based upon peripheral blood count recovery and the clinician's judgment) and remission status assessed at this later time point.

For lymphoma patients, if the bone marrow was M1 marrow with negative MRD at the beginning of the block 1, repeat bone marrow aspiration/biopsy was not necessary.

Primary efficacy variables

The primary endpoint to determine efficacy was response (CR + CR MRD-, and CR + CR MRD- + CRi) after 1 cycle of therapy.

Acceptability and palatability of ixazomib formulations

The acceptability and palatability performance of the drug product were investigated using a questionnaire that was administered to the patients or their parents/guardians.

Sample size

Sample size for the Phase 2 expansion was 12-18 response evaluable patients, including the response evaluable patients treated at the RP2D and enrolled in the Phase 1.

Randomisation and blinding (masking)

Study T2017-002 was an open-label, uncontrolled study.

Statistical Methods

Frequency and rate of the DLTs and toxicities were summarized by dose level. Summary of toxicities were broken down by grade and attribution. Response (CR + CR MRD- or CR + CR MRD- + CRi) were tabulated with the number and percentage of the evaluable patients.

Protocol amendments

The study protocol was amended seven times. The main changes introduced by study amendments are summarised below:

Amendment 1 (19-Dec-2019)

- mercaptopurine dose adjustments were made to allow for genotype variations in either TPMT or NUDT15
- a neurological exam was added to be performed prior to each ixazomib dosing
- response definitions were amended to replace CRp category with CRi and divide the CR category to include CR MRD-

Amendment 2 (16-Sep-2020)

- dose Limiting Toxicity: changed platelet criteria for hematological toxicity definition to platelet ≥ 20.000/µL, platelet infusion independent and length of evaluation time to 49 days.

Amendment 3 (11-May-2021)

- the definition of what chemotherapy regimens and drugs and dosages (i.e. maintenance therapy drugs) were allowed prior to enrolment and what length of washout was required for the drugs and biologics was clarified
- introduced flexibility in the timing of chemotherapy administration, including the timing of Day 29 IT therapy, allowing for up to 72 hours flexibility for scheduling or other issues

Amendment 4 (24-Jan-2022)

- it was clarified that DS and infants (<1 year of age) would enrol to Phase 2 at Dose Level 1. Their data would only be descriptive and not included in DLT and response evaluation
- crisantapase or recombinant asparaginase Erwinia chrysanthemi were included as substituted for allergy to Pegaspargase
- clarification that administration of ixazomib capsules should vbe rounded to the nearest 0.2mg was introduced

Amendment 5 (26-Oct-2022)

- revised eligibility criteria to read "Patients must be < 22 years of age at time of enrolment."
- revised eligibility criteria for prior therapeutic attempts for B cell ALL/LLy patients from failed two or more prior attempts to failed one or more prior attempts

- revised exclusion criteria to include allergy or intolerance to Calaspargase
- added calaspargase to treatment schedule for Block 1 and Block 2. Added footnote that regarding the administration of either pegaspargase or calaspargase according to current approved labeling based on age and regional availability. Added dosage administration for calaspargase to be only administered once per cycle and on Day 2 for Block 1 and Day 9 or 10 for Block 2.

Amendment 6 (20-July-2023)

- revised definition of a patient evaluable for response to include those who died as a result of a DLT and that such patients were to be considered as non-responder. Also added that patients who were not considered evaluable for response were to be replaced.

- clarified that the occurrence of a toxic death was to be defined as a death occurring anytime during protocol therapy or until 30 days following the last dose of study therapy
- added new Non-responder (NR) response criteria

Amendment 7 (07-Sep-2023)

- the Toxicity/Adverse Events section was changed to reflect recent updates in the Ixazomib Investigator's Brochure edition 15

Results

Participant flow

At the time of the completion of this Phase 2 study, twenty patients (including six patients from Phase 1 who were treated at Dose Level 2) had enrolled onto the study (see Table below). All twenty received study treatment and eighteen patients completed at least one cycle. Two patients died due to toxicities prior to their cycle 1 disease assessment and were non-evaluable for response.

Table 10-1 Disposition of patients enrolled

Dose Level	Dosage of ixazomib	Enrolled	Completed at least one cycle of Study Treatment	Continued to follow-up
2 (RP2D)	2 mg/m^2/day	20⌘	18[1]	18[1]

⌘This includes 6 patients enrolled in the Phase I portion, who were treated at RP2D. It also includes 18 patients that completed at least one cycle of study treatment and had a response assessment.

[1]Two patients were considered non-evaluable due to infectious deaths early in therapy

No patients discontinued or withdrew from the study after enrollment.

Recruitment

Overall, 20 patients were enrolled in the Phase 2 part of study T2017-002 at ten centres within the United States of America, including 6 patients who initially received ixazomib at RP2D in Phase 1. The first patient was enrolled on Jan 26, 2020 and the last patient completed study procedures on Dec 03, 2023.

Baseline data

Of the overall cohort of 20 patients, the median age at study entry was 8.2 years, with the majority of patients (60%) ages 2 to less than 12 years; males comprised 55% of the study population, and 55% were white.

Average number of failed treatment attempts, as defined by refractory to therapy (failure to achieve remission) or relapsed disease (achieved remission but then suffered a recurrent of disease), prior to study entry was 2.5; with 6 patients having failed 1 prior attempt, 4 patients having failed 2 prior attempts, 6 patients having failed 3 prior attempts, and 4 patients having failed more than 3 prior attempts. A total of 16 patients were reported to have a bone marrow status of M3 (≥25% blasts) prior to study entry, however minimal residual disease (MRD) data was not available for 6 of the patients. Evidence of circulating blasts was present in a total of 14 patients at study entry, while 3 patients had evidence of extramedullary disease at study entry.

Number analysed

The cohort for response results presented in this section comprises 18 patients who completed at least 1 treatment cycle and were evaluable for response. All 18 patients were assessed for the presence of bone marrow blasts, minimal residual disease (MRD), evidence of circulating blasts, extramedullary lesions (for lymphoma patients), and evidence of extramedullary disease.

Infants less than 1 year of age and Down syndrome patients (Strata B) were excluded from the response evaluation for efficacy analysis due to their unique biology and toxicity profile.

No Down syndrome patients or infants (<1 year of age) were treated at Dose Level 2.

Efficacy results

In the overall cohort of 18 patients, the best response was demonstrated in 66.6% (95%CI 41.0, 86.7), which included CR rate of 11.1%, CR MRD- rate of 33.3%, and Cri rate of 22.2% (see Table below).

Table 2.a Measurement of response for all patients evaluable for response

Response	DL2 (2.0 mg/m^2/day) N = 18 n (% [95% CI])
Complete Remission (CR)	2 (11.1% [1.38, 34.7])
Complete Remission, MRD negative (CR MRD-)	6 (33.3% [13.3, 59.0])
Complete Remission with Incomplete Count Recovery (CRi)	4 (22.2% [6.4, 47.6])
Partial Response (PR)	2 (11.1% [1.38, 34.7])
Stable Disease (SD)	1 (5.6% [0.141, 27.3])
Progressive Disease (PD)	2 (11.1% [1.38, 34.7])
Non-responder	1 (5.6% [0.141, 27.3])

DL: dose level.

Palatability of ixazomib

The reported data included acceptability/palatability assessments for a total of 36 doses of ixazomib liquid formulation via oral syringe:

• 12 doses (33%) reported on by patients

• 24 doses (66%) reported on by parents.

Overall, there was considerable inter- and intra-reporter variability in the acceptability/palatability of the doses. However, acceptability/palatability was assessed as positive or neutral in the majority of doses, as reported by patients and parents, respectively:

• 83% and 67% of doses tasting good, somewhat good, or OK

• 92% and 71% of doses smelling good, somewhat good, or OK

• 75% and 53% of doses not having an aftertaste

• 75% and 79% of doses being easy, somewhat easy, or OK to take.

Safety results

Extent of Exposure

The planned dose of oral ixazomib in phase 2 of the study was the RP2D, 2.0 mg/m^2/dose, administered on Days 1, 4, 8, and 11. All 20 patients received this dose. Treatment cycle 1 was stopped for 2 of the 20 patients because they died during treatment. The remaining 18 patients received at least 1 complete cycle of treatment.

Adverse Events (AEs)

Dose-Limiting Toxicities

Two of the AEs experienced in the 20 patients met the criteria for a DLT:

• Grade 3 enterocolitis (Grade 3 during the treatment cycle; then progressed and resulted in the patient's death 1 month later) deemed possibly related to ixazomib and possibly related to the backbone therapy.

• Grade 4 typhlitis deemed probably related to both ixazomib and the backbone regimen.

Treatment-Emergent Adverse Events (TEAEs)

All 20 patients in the safety population had at least 1 TEAE (any grade), at least 1 ≥ Grade 3 TEAE, and at least 1 treatment-related TEAE—with each patient having at least 1 ≥ Grade 3 TEAE related to ixazomib and at least 1 ≥ Grade 3 TEAE related to the chemotherapy backbone alone (see Table below).

Table 3.a Overview of TEAEs—Safety Population

	Number of Patients (%) (N=20)
At least 1 TEAE	20 (100)
Grade 3 or higher	20 (100)
Treatment-related [a]	20 (100)
Grade 3 or higher related to ixazomib	20 (100)
Grade 3 or higher related to chemotherapy backbone only	20 (100)
Leading to permanent study drug discontinuation	3 (15)
At least 1 serious TEAE	16 (80)
Treatment-related [a]	14 (70)
On-treatment death	2 (10)

TEAE: treatment-emergent adverse event.
[a] Related to either ixazomib or chemotherapy backbone.

The most common TEAEs (reported by ≥6 patients) regardless of grade or relationship to treatment are shown in Table below.

Table 3.b Most Common (≥6 Patients) TEAEs—Safety Population

	Number of Patients (%) (N=20)
Hyponatremia	18 (90)
Hypoalbuminemia	15 (75)
AST increased	15 (75)
Hypocalcemia	15 (75)
Hyperglycemia	14 (70)
ALT increased	14 (70)
Hypophosphatemia	14 (70)
Vomiting	12 (60)
Hypokalemia	12 (60)
Nausea	11 (55)
Blood bilirubin increased	10 (50)
Febrile neutropenia	9 (45)
Hyperphosphatemia	9 (45)
Sinus tachycardia	9 (45)
Abdominal pain	8 (40)
Mucositis oral	8 (40)
Anorexia	7 (35)
Fever	7 (35)
Diarrhea	7 (35)
Hyperkalemia	7 (35)
Hypermagnesemia	7 (35)
APTT prolonged	6 (30)
Hypoglycemia	6 (30)
Sepsis	6 (30)
Hypertension	6 (30)
Hypomagnesemia	6 (30)

ALT: alanine aminotransferase; APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; TEAE: treatment-emergent adverse event.

A total of 75% or more of patients had hyponatremia, hypoalbuminemia, aspartate aminotransferase increased, and/or hypocalcaemia.

Eighteen infectious events were reported; sepsis was the most common, occurring in 6 of the 20 patients (30%), followed by skin infection (2/20) and enterocolitis infection (2/20).

Table 3.c Infection Events Reported in More Than 1 Patient—Safety Population

	Number of Patients (%) (N=20)
Sepsis	6 (30)
Enterocolitis infection	2 (10)
Skin infection	2 (10)

Grade 3 or higher TEAEs reported in more than 1 patient are shown in Table below; anaemia was the most common, occurring in 15 of the 20 patients (75%).

Table 3.d Grade 3 or Higher TEAEs Reported in More Than 1 Patient—Safety Population

	Number of Patients (%) (N=20)
Anemia	15 (75)
ALT increased	9 (45)
Febrile neutropenia	9 (45)
AST increased	8 (40)
Hypokalemia	6 (30)
Mucositis oral	5 (25)
Hyperglycemia	3 (15)
Hypoalbuminemia	3 (15)
Sepsis	3 (15)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; TEAE: treatment-emergent adverse event.

Sixteen patients had at least 1 treatment-emergent SAE, of whom 14 had a treatment-related SAE (related to either ixazomib or chemotherapy backbone, see Table below).

Table 3.e Treatment-Related SAEs, by Severity, Reported in More Than 1 Patient—Safety Population

	Number of Patients (%) (N=20)		
	Grade 3	Grade 4	Grade 5
AST increased	7 (35)	0	0
ALT increased	6 (30)	1 (5)	0
Febrile neutropenia	6 (30)	0	0
Sepsis	3 (15)	2 (10)	1 (5)
Hypokalemia	3 (15)	2 (10)	0
Hyperkalemia	2 (10)	2 (10)	0
Mucositis oral	2 (10)	1 (5)	0
Hyperglycemia	2 (10)	0	0
Hypertension	2 (10)	0	0
Hypoalbuminemia	2 (10)	0	0

ALT: alanine aminotransferase; AST: aspartate aminotransferase; SAE: serious adverse event.
Treatment-related indicates related to either ixazomib or the chemotherapy backbone.

Based on the AE dataset, 3 patients had at least 1 TEAE (all grades) leading to permanent discontinuation of study treatment as follows:

- A patient in dose level 2 experienced a grade 5 enterocolitis and grade 3 hypophosphatemia event during Treatment Cycle 1. The grade 5 event led to the death of the patient after the completion of Cycle 1

- A patient in dose level 2 experienced a grade 4 sepsis and typhlitis event in Treatment Cycle 1. Several doses of ixazomib were held to allow the patient to recover. The patient was later removed from study treatment due to these events.
- A patient in dose level 2 experienced a grade 5 oedema cerebral event and died due to brain death on their last day of study therapy on Day 13 of Treatment Cycle 1.

Based on the AE dataset, 2 patients had at least 1 TEAE (all grades) leading to dose interruption as follows:

- A patient in dose level 2 presented with fever related to adenovirus which later developed into febrile neutropenia (unrelated to study treatment) on Day 2 of Cycle 1. The Day 2 administration of Pegaspargase as part of the chemotherapy backbone was interrupted and resumed the following day. The patient was administered cefepime and vancomycin and the fever and febrile neutropenia resolved the following day.
- A patient in dose level 2 began experiencing a grade 4 adult respiratory distress syndrome and grade 3 hyperkalaemia during treatment block 1 which led to the withholding of the Day 22 vincristine for Treatment Cycle 1.

Based on the AE dataset, 2 patients had at least 1 TEAE (all grades) leading to dose modification as follows:

- A patient in dose level 2 developed an allergic reaction to Pegaspargase when administered intravenously on Day 2 of Cycle 1. Soon after the Pegaspargase was started, the patient complained of throat tightness and Pegaspargase was immediately stopped. Patient was given IV Benadryl and the adverse reaction was quickly alleviated. As part of this study design, Erwinia asparaginase was substituted in the event of allergic reaction to Pegaspargase.
- A patient in dose level 2 developed a grade 3 AST increase after the start of Treatment Cycle 1. The patient restarted treatment at Dose Level 1.

Deaths

Seven of the 20 patients (35%) died either during treatment or during the post-treatment 2-year follow-up period. Two patients died during treatment: 1 from septic shock and the other from oedema cerebral/sepsis. The remaining 5 patients died during the post-treatment period: 1 from enterocolitis and 4 from disease progression. This mortality rate is not unexpected, given the toxic nature of the treatment and the frail nature of these paediatric patients with relapsed and/or refractory disease.

2.3.3. Discussion on clinical aspects

The MAH has submitted this application in accordance with Article 46 of regulation 1901/2006 to provide results from the Phase 2 part of study T2017-002 (PIP study 4). Study T2017-002 investigated the addition of ixazomib (Ninlaro) to standard re-induction chemotherapy in children with relapsed or refractory acute lymphoblastic leukaemia/lymphoma (R/R ALL). Preliminary results from the Phase 1 portion of study T2017-002 have already been assessed in procedure EMEA/H/C/003844/P46/012.

ALL is the most common malignancy in children, with approximately 40 cases per million diagnosed each year in the EU, and a peak incidence occurring between 0 and 5 years of age (Parkin DM et al, WHO Fact Sheet 2009).

Despite progressive advancements with the introduction of multi-drug chemotherapy regimens and allogeneic haematopoietic stem cell transplant (alloHSCT), resulting in a cure rate of ~90% in

industrialised countries (see e.g. Hunger SP et al, NEJM 2015), ALL treatment remains complex, prolonged and associated with significant short- and long-term toxicity.

Moreover, the outcomes of children with ALL who experience relapse (especially early relapse) or have refractory disease remain unsatisfactory, with only ~50% achieving long-term survival (see e.g. Hunger SP et al, Blood 2020).

Research efforts in the last years have been focused on improving the efficacy of R/R ALL therapy. The claim of all "re-induction" regimens is to achieve a second complete remission (CR2) with undetectable minimal residual disease (MRD-): reaching a deep response is, in fact, the necessary prerequisite to maximise clinical benefit from subsequent alloHSCT. Most re-induction regimens used in clinical practice are based on a "standard" four-drug chemotherapy backbone, which includes corticosteroids, vincristine, an anthracycline/mitoxantrone and an asparaginase. Drugs, doses and schedules are known to vary across cooperative group protocols.

With the possible exceptions of subjects with late/isolated extramedullary relapse who reach MRD negativity after re-induction, in fact, most children with R/R ALL who achieve CR2 still need to undergo further "consolidation" with alloHSCT in order to improve their chances for long-term disease control/cure. The importance of improving the efficacy of re-induction regimens lies in the fact that the best results with alloHSCT consolidation are achieved in patients who are MRD negative before transplant (see e.g. Merli P et al, Front Pediatr. 2021).

Several attempts have been made over the years to improve the efficacy of re-induction regimens by adding novel agents to the standard chemotherapy backbone, although no recognised clinical standard has still emerged (see e.g. Bride KL et al, Blood 2018; Pikman Y et al. Clin Cancer Res 2017; Khaw SL et al, Blood 2016).

In line with this paradigm, Phase 1-2 study T2017-002, an open-label, non-randomised, dose-finding/dose-expansion study, was designed by the TACL (*Therapeutic Advances in Childhood Leukemia/Lymphoma*) consortium to investigate the safety and efficacy of ixazomib (Ninlaro), in addition to a standard four-drug re-induction regimen, in children with R/R ALL.

Overall, as already discussed (see procedure EMEA/H/C/003844/P46/012), the rationale for combining PIs with standard re-induction chemotherapy can be understood based on both pre-clinical data, which supported a possible synergistic activity of PIs and conventional chemotherapy agents in ALL (see e.g. Koyama D, et al. Leukemia. 2014; Cheung LC et al, Front Oncol. 2021; Roeten MSF et al, Cells. 2021), and preliminary clinical evidence with bortezomib (see e.g. Horton TM et al, Br J Haematol 2019).

Preliminary safety and efficacy data from the phase I part of study T2017-002 (PIP study 2, see procedure EMEA/H/C/003844/P46/012) were also encouraging and supported further investigation.

In Phase 2, ixazomib at the RP2D (i.e. 2 mg/m^2 for children aged ≥ 1 year; 0.07 mg/kg/day for children aged < 1 year) was administered on days 1, 4, 8 and 11 in addition to a VXLD (vincristine, dexamethasone, pegaspargase/calaspargase and doxorubicin) re-induction chemotherapy regimen. Doxorubicin was preferred to mitoxantrone because of the increased toxicity observed with mitoxantrone and dexamethasone in previous add-on studies (see e.g. Rheingold SR et al, Br J Haematol 2017). This is understood and acceptable.

After re-induction, subjects who achieved disease remission could either receive further consolidation according to the UK ALL R3 chemotherapy Block 2 regimen (with ixazomib administered at the RP2D on days 1, 4, 8, 15 and 18) followed by maintenance (with ixazomib administered each cycle on days 1, 8 and 15), or undergo alloHSCT. Limited data were available, however, for the consolidation/maintenance phase, since the vast majority of patients in study T2017-002 did not proceed beyond re-induction.

Ixazomib could be administered either in the oral formulation (hard capsules) or as powder for solution for injection reconstituted for oral (via oral syringe) or gastric (via nasogastric tube) administration. In this regard, a summary report on the acceptability/palatability of the liquid formulation, focused on data obtained using a questionnaire administered to the patients or their parents/guardians, was provided by the MAH. A total of 12 patients received at least 1 dose of the ixazomib liquid formulation: 10 via oral syringe and 2 via nasogastric tube, and a total of 37 doses have been administered. Acceptability/palatability was assessed as positive or neutral in the majority of doses, reported as:

• tasting good, somewhat good, or OK (26/37 [70%])

• smelling good, somewhat good, or OK (28/37 [76%])

• not having an aftertaste (19/37 [51%])

• being easy, somewhat easy, or OK to take (28/37 [76%]).

The 10 patients in Study T2017-002 who received at least 1 dose of the ixazomib liquid formulation orally and completed the acceptability/palatability questionnaire gave responses that were quite variable, both among patients and across the 4 doses administered per patient, thus no firm conclusions could be inferred. However, it is noted that acceptability/palatability of the orally administered liquid ixazomib formulation was assessed as positive or neutral for the majority of doses, with response distributions generally consistent between patient-reported and parent-reported data. The variability of the findings is considered understandable in light of the small number of patients and doses in this exploratory study, and also considering that the acceptability testing differed depending on patient. The MAH evaluation is, therefore, considered acceptable and no concern is raised.

The study inclusion/exclusion criteria in PIP study 4 were overall adequate to identify a study population comprising children and young adults aged ≤ 21 years with R/R ALL in morphological relapse (i.e. with ≥ 5% blasts by morphology) with or without extramedullary disease. Patients with CNS involvement (CNS2 and CNS3) were allowed and received standard IT treatment: this is in line with clinical practice and acceptable, since target tissue delivery in CNS has been confirmed for ixazomib (see e.g. Quillin J et al, Mol Clin Oncol. 2020).

Subjects with isolated CNS or testicular disease were excluded, which is reasonable considering their different prognosis and treatment standard, as well as patients with mixed phenotype of mature B (Burkitt) leukemia, which is also agreed considering the significant differences in terms of disease biology and therapy. On the other hand, patients could be enrolled independently of genetic characteristics (e.g. both Philadelphia chromosome positive and negative ALL were allowed) and type and duration of response to prior treatments. Although high heterogeneity could be anticipated, this was acceptable considering the exploratory nature of the trial. The interpretation of results in terms of clinical benefit is, however, necessarily limited.

The primary endpoint for efficacy was the rate of "CR + CR and MRD-", and "CR + CR and MRD- + CRi" after 1 cycle of therapy, which is in line with the main objective of study T2017-002 (i.e. characterising the short-term efficacy of the proposed ixazomib + VXLD re-induction platform) and acceptable considering the uncontrolled study design. No information was available, however, on response duration and other measures of long-term clinical benefit, nor on transplant access. The definitions of CR/CRi and MRD negativity in the study protocol were standard and acceptable as measures of depth of cytoreduction: the rules for BM aspiration timing and evaluation were also in line with the current recommendations at the time the study was designed.

The pre-specified sample size for the Phase 2 efficacy expansion cohort (n=12-18) was, however, too limited to draw any reliable information, especially when the high biological and clinical heterogeneity of ALL is taken into account. Moreover, the decision to include in the Phase 2 cohort also subjects who

received ixazomib at the RP2D dose in Phase 1 farther reduced the "confirmatory" value of data from the expansion phase, since the principle of independent replication of the results is severely hampered.

The study protocol was repeatedly amended during the conduction of study T2017-002, which is not unexpected in light of the exploratory nature of the trial. However, protocol amendments introduced progressive changes in relevant study aspects such as patient selection (e.g. age at enrolment), response definition, toxicity assessment and type of drugs (e.g. possibility to administer asparaginase from Erwinia chrysanthemi or calaspargase) and timing of their administration. Such relevant changes in an ongoing trial further complicated data interpretation.

Twenty patients were eventually enrolled in the Phase 2 part of study T2017-002 at 10 centres in the US, with 6/20 having actually received ixazomib at the proposed RP2D dose in Phase 1. Limited baseline characteristics were provided: median age was 8.2 years (with 60% of patients aged 2 to 12 years) and male sex was slightly prevalent (55%) in the study population. The mean number of prior treatments was 2.5, yet high heterogeneity could be observed, with 6 (30%) patients who received ixazomib as their 2nd line treatment, and 7/20 (35%) who had at least 3 prior lines of therapy. Three patients had extramedullary disease at study entry, while no data have been reported on cytogenetics (e.g. bcr-abl status) or leukemic blast cell line (e.g. B or T cell ALL).

Only 18/20 patients were considered evaluable for response in the primary analysis, since two patients died because of toxicity before the planned disease assessment at the end of cycle 1. From a conservative perspective, however, those two patients should be included in the response analysis as non-responder.

The overall remission rate (CR + CR MRD- + CRi) was 66% (95%CI 41.0, 86.7), which was lower than that observed in Phase 1 (77.8%, see procedure EMEA/H/C/003844/P46/012), despite 6/20 Phase 2 patients were actually treated in Phase 1. When the two subjects who were excluded from the primary efficacy analysis because of early death are considered as non-responder, the overall remission rate is 60%. The CR + MRD- rate (optimal response) in the primary analysis was 33% (95%CI 13.3, 59.0), which was also lower than that observed in Phase 1 (44.4%). No data were reported on alloHSCT access or response duration.

Overall, the limited efficacy data provided by the MAH are of difficult interpretation: although complete remissions (including deep responses with no detectable residual disease) have been observed, contextualising the reported CR rate in the current therapeutic context is not straightforward, because of the limited sample size, lack of controls, high heterogeneity (especially in terms of prior treatment) and lack of relevant cytogenetic/biologic data. The extent of the contribution of ixazomib to the overall efficacy of the re-induction regimen is, therefore, unknown.

With respect to safety, all subjects in study T2017-002 experienced at least 1 treatment-emergent adverse event (TEAE) and at least 1 grade ≥ 3 TEAE, and serious TEAEs were reported in 80% of subjects. This significant toxicity is not unexpected when the side effects of the VXLD chemotherapy backbone and the signs/symptoms of the underlying malignancy are considered. Despite all subjects had at least 1 Grade ≥ 3 TEAE deemed related to ixazomib, disentangling the contribution of each component of the ixazomib + VXLD re-induction regimen to the observed toxicity is not possible in the absence of controls.

The most common TEAEs reported in Phase 2 were related to electrolyte imbalances (e.g. hyponatraemia 90%, hypocalcaemia 75%, hypophosphataemia 70%, hypokalaemia 60%, hyperphosphataemia 45%, hyperkalaemia and hypermagnesaemia 35%, hypomagnesaemia 30%), signs of hepatotoxicity (e.g. hypoalbuminaemia 75%, AST increased 75%, ALT increased 70%, blood bilirubin increased 50%, APTT prolonged 30%), impaired glucose metabolism (hyperglycaemia 70%, hypoglycaemia 30%), infections (febrile neutropenia 45%, fever 35%, sepsis 30%) and gastro-intestinal (GI) symptoms (vomiting 60%, nausea 55%, abdominal pain 40%, anorexia and diarrhoea 35%). Electrolyte imbalances and glucose

metabolism alterations are not uncommon when dexamethasone is administered at high doses and for a prolonged period of time, while hepatotoxicity, infections and GI adverse events can also be imputed to dose-dense chemotherapy. On the other hand, infections (especially upper respiratory tract infection and bronchitis), GI disorders (e.g. diarrhoea, nausea, vomiting) and liver impairment (including enzyme changes) have also been reported with ixazomib (see the Ninlaro SmPC, Section 4.8); in the absence of controls, reliable causal relationship evaluations could not be performed.

The most commonly reported severe (Grade ≥3) TEAEs included anaemia (75%), febrile neutropenia (45%), ALT (45%) and AST increased (40%), oral mucositis (25%) and electrolyte imbalances. A similar pattern could also be observed for SAEs. Death events were reported for 2 subjects during the treatment phase (1 septic shock and 1 cerebral oedema in the context of sepsis), and for 5 subjects in the post-treatment period (1 enterocolitis whose onset occurred during treatment and 4 deaths due to disease progression).

Overall, the toxicity profile of the ixazomib + VXLD combination can be considered consistent with what expected with multi-drug dose-dense chemotherapy. However, limited sample size and lack of controls did not allow to exclude a significant contribution of ixazomib to the overall toxicity.

3. Rapporteur's overall conclusion and recommendation

The pharmacologic rationale to explore the addition of PIs to a standard re-induction chemotherapy platform for R/R ALL is understood. In this regard, in 2015 clinical data with bortezomib plus chemotherapy were submitted in accordance with Article 46 of Regulation (EC) No1901/2006 and led to the update of sections 4.2 and 5.1 of the Velcade SmPC (see procedure EMEA/H/C/000539/II/0079).

In agreement with the PIP, the MAH of Ninlaro has submitted updated clinical data from the Phase 2 part of study T2017-002, which investigated the efficacy and safety of an ixazomib + VXLD re-induction regimen in children with R/R ALL.

Overall, efficacy data showed that the addition of ixazomib to standard re-induction chemotherapy resulted in an overall remission rate (CR + CR MRD- + CRi) of 66%, with a 33% CR + MRD-. However, no data on response duration nor on alloHSCT access were provided, which hampered any evaluation of long-term clinical benefit. Further, the observed toxicity profile of the ixazomib + VXLD regimen was not negligible, including severe, serious and fatal TEAEs that comprised infections, electrolyte imbalances, liver toxicity, impaired glucose metabolism and gastro-intestinal toxicity.

As stated by the MAH, in the last years the treatment landscape of paediatric R/R ALL has significantly changed to include effective anti-CD19 immunotherapy options, such as tisagenlecleucel (a CAR T cell ATMP) and blinatumomab (the first-in-class anti-CD19/CD3 bispecific T cell engager). In this new therapeutic context, the clinical relevance of the preliminary results observed in exploratory study T2017-002 is uncertain. Moreover, clinical data from study T2017-002 are of difficult interpretation, since limited numbers, high heterogeneity and lack of controls did not allow to evaluate the actual contribution of ixazomib to the efficacy and toxicity of the investigated ixazomib + VXLD combination regimen. Therefore, although it cannot be excluded that ixazomib in addition to a standard multi-drug re-induction platform might be of relevance, especially in some clinical setting (e.g. for patients who failed anti-CD19 immunotherapy, or for CD19-negative ALL subtypes, such as T-cell ALL), the available data are considered too limited to provide any valuable information. The MAH's conclusions that no changes in the Ninlaro SmPC can be currently recommended are, therefore, agreed, and further data from randomised, controlled trials are needed to assess the actual value of ixazomib in the treatment of paediatric R/R ALL.

☒ **Fulfilled:** No regulatory action required.

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

N/A

Clinical studies

Product Name: Ninlaro Active substance: ixazomib

Study title	Study number	Date of completion	Date of submission of final study report
Uncontrolled, open label study to assess pharmacokinetics and safety of ixazomib capsules for oral use, and of powder for solution for injection, oral use and gastric use, in paediatric patients from birth to less than 18 years of age (and adults if diagnosed at less than 18 years of age) with relapsed/refractory acute lymphoblastic leukaemia or lymphoblastic lymphoma with or without extramedullary disease **Phase 1 portion of study T2017-002**	T2017-002	18 May 2021	15 November 2021
Uncontrolled, open label study to assess pharmacokinetics and safety of ixazomib capsules for oral use, and of powder for solution for injection, oral use and gastric use, in paediatric patients from birth to less than 18 years of age (and adults if diagnosed at less than 18 years of age) with relapsed/refractory acute lymphoblastic leukaemia or lymphoblastic lymphoma with or without extramedullary disease **Phase 2 portion of study T2017-002**	T2017-002	3 December 2024	11 June 2024*
Randomised, controlled, open-label study to assess event free survival (EFS) of patients from birth to less than 18 years of age (and adults if diagnosed at less than 18 years of age) with relapsed or refractory (RR) acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LLy) with or without extramedullary disease treated with ixazomib in combination with vincristine, dexamethasone, L-asparaginase, and doxorubicin (VXLD) chemotherapy versus VXLD chemotherapy alone	Not yet available	By Dec 2029	Within 6 months of study completion
Randomized, controlled study of modified augmented Berlin-Frankfurt-Münster (ABFM) regimen with bortezomib during induction/consolidation and intensification followed by maintenance therapy with/without ixazomib in patients from birth to less than 18 years of age (and adults if diagnosed at less than 18 years of age) with newly diagnosed ALL or LLy with or without extramedullary disease	Not yet available	By Dec 2031	Within 6 months of study completion

*Agreed submission date with EMA on 29 May 2024