EMADOC-1700519818-2738249
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure No. EMA/VR/0000315309

Invented name: Kisqali

International non-proprietary name: ribociclib

Note

Variation 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	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Submission deadline	28 Nov 2025	26 Nov 2025	☐
☐	Validation	28 Dec 2025	9 Dec 2025	☐
☐	Start date	29 Dec 2025	29 Dec 2025	☐
☐	CHMP Rapporteur AR	2 Feb 2026	27 Jan 2026	☐
☐	CHMP comments	16 Feb 2026	16 Feb 2026	☐
☐	Updated CHMP Rapporteur AR	19 Feb 2026	19 Feb 2026	☐
☐	Request for supplementary information	26 Feb 2026	26 Feb 2026	☐
☐	Response submission	3 Mar 2026	3 Mar 2026	☐
☐	Re-start	4 Mar 2026	4 Mar 2026	☐
☐	CHMP Rapporteur AR	11 Mar 2026	5 Mar 2026	☐
☐	CHMP comments	16 Mar 2026	16 Mar 2026	☐
☐	Updated CHMP Rapporteur AR	19 Mar 2026	N/A	☐
☒	CHMP opinion	26 Mar 2026	26 Mar 2026	☐

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 26 November 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		Type
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II

Update of sections 4.2, 5.1, and 5.2 of the SmPC in order to update information on paediatric population based on the final results from the study CLEE011Q12101 listed as study 3 of the PIP EMEA-002765-PIP02-21-M01 for Kisqali; this is a Phase I/II interventional study CLEE011Q12101 designed to determine a safe dose and treatment schedule of ribociclib when combined with TOTEM, with an aim to provide a therapeutic opportunity for paediatric patients with high unmet medical need, especially those with relapsed or refractory high-risk Neuroblastoma.

The requested variation proposed amendments to the Summary of Product Characteristics.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0266/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0266/2024 was completed.

The PDCO issued an opinion on compliance for the PIP P/0266/2024.

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

Ribociclib (Kisqali) is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6. These kinases are activated upon binding to D-cyclins and play a crucial role in signalling pathways which lead to cell cycle progression and cellular proliferation. The cyclin D-CDK4/6 complex regulates cell cycle progression through phosphorylation of the retinoblastoma protein (pRb).

Kisqali was first approved in the EU on 22 August, 2017. The currently approved indications are:

Early breast cancer

Kisqali in combination with an aromatase inhibitor is indicated for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer at high risk of recurrence (see section 5.1 for selection criteria).

In pre- or perimenopausal women, or in men, the aromatase inhibitor should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

Advanced or metastatic breast cancer

Kisqali is indicated for the treatment of women with HR-positive, HER2-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy.

In pre- or perimenopausal women, the endocrine therapy should be combined with a LHRH agonist.

This type II variation application concerns the submission of the study report for phase 1 – Cohort A of the paediatric study CLEE011Q12101.

This study is included in the PIP EMEA-002765-PIP02-21-M01 for Kisqali and aimed to determine a safe dose for ribociclib in combination with topotecan and temozolomide (TOTEM) in paediatric patients with high unmet medical need, especially those with relapsed or refractory (r/r) high-risk Neuroblastoma (NB).

The study was planned to be a phase 1/2 study. Phase 1 was to include paediatric patients with different solid tumours and consisted of an initial dose-finding part (phase 1 – Cohort A) and a dose expansion part (phase 1 – Cohort B), with the aim to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D). Phase 1 was to be followed by a phase 2, to determine the efficacy and safety in paediatric patients with r/r high-risk NB.

An MTD could, however, not be determined due to dose-limiting toxicity (DLT) at all three investigated dose levels and schedules in phase 1 – Cohort A. Furthermore, no objective responses were observed in any of the 12 enrolled and dosed subjects.

The combination treatment of ribociclib with TOTEM was concluded to be intolerable in paediatric patients, leading to DLTs in 6 participants (2 per dose cohort) and high grade haematological adverse events (AEs) in the majority of the participants. It was not considered fruitful to study additional dose schedules. In line with the stopping rule outlined in the protocol, the Sponsor terminated the study and no additional subjects were enrolled.

Therefore, the MAH suggests that the data generated does not support further investigation of ribociclib for the intended paediatric indication *"treatment of relapsed or refractory NB in patients aged 12 months and above in combination with temozolomide and topotecan"* as stated in the PIP.

This conclusion is agreed and the PIP can be considered completed in terms of Clinical Study 3.

No new safety signals were identified during the conduct of the trial, although safety data should be interpreted with caution due to the limited number of patients. The most commonly reported AEs were haematological and gastrointestinal toxicities, as anticipated with the combination treatment, ribociclib and TOTEM. The most commonly reported DLTs related to haematological toxicity (Grade 4 neutropenia, Grade 3 anaemia). One subject had Grade 4 dyspnoea and subsequently died due to respiratory failure, which was suspected to be treatment-related.

With the current application the MAH proposed updates to sections 4.2, 51 and 5.2 of the SmPC to reflect the results of study CLEE011Q12101. No updates are proposed for the PL. The proposed updates are agreed.

The benefit/risk of Kisqali in the approved indications remains positive.

3. Recommendations

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

Variation(s) requested		**Type**
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II

Update of sections 4.2, 5.1, and 5.2 of the SmPC based on the final results from paediatric study CLEE011Q12101 in order to complete the PIP (P/0266/2024) and in order to fulfil Article 46 of Regulation EC No 1901/2006; study CLEE011Q12101 is a phase I/II interventional study designed to determine a safe dose and treatment schedule of ribociclib when combined with topotecan and temozolomide (TOTEM), with an aim to provide a therapeutic opportunity for paediatric patients with high unmet medical need, especially those with relapsed or refractory high-risk neuroblastoma.

☒ is recommended for approval.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0266/2024 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex I are recommended.

4. EPAR changes

The table in the 'Steps after' module of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Section 4.2 'Posology and method of administration' of the SmPC

Special populations

[…]

Paediatric population

The safety and efficacy of Kisqali in children and adolescents aged below 18 years have not been established. Currently available data on Kisqali in combination with topotecan and temozolomide (TOTEM) in paediatric patients are described in sections 5.1 and 5.2, but no recommendation on a posology can be made.

Section 5.1 'Pharmacodynamic properties' of the SmPC

Paediatric population

Study CLEE011Q12101

A phase I/II multicentre study was conducted to evaluate the efficacy and safety of the combination of ribociclib with TOTEM in paediatric (4 to <18 years, n=10) and young adult (18 to 20 years, n=2) patients with relapsed or refractory (r/r) neuroblastoma (NB) or other solid tumours (including alveolar rhabdomyosarcoma/rhabdomyosarcoma, malignant glioma, malignant astrocytoma, glioblastoma and

medulloblastoma). Three cohorts were completed in the phase I dose-finding part which investigated the following dose regimens in a 28-day treatment cycle: ribociclib 200 mg/m²/day (days 1 to 21) plus topotecan 0.75 mg/m²/day and temozolomide 150 mg/m²/day (days 1 to 5) (concurrent dosing); ribociclib 100 mg/m²/day (days 6 to 21) after topotecan 0.75 mg/m²/day and temozolomide 150 mg/m²/day (days 1 to 5) (sequential dosing); ribociclib 100 mg/m²/day (days 1 to 14) plus topotecan 0.75 mg/m²/day and temozolomide 100 mg/m²/day (days 1 to 5) (concurrent dosing). Patients had a median age of 14 years (n=12), 7 were female. No objective response was observed. The maximum tolerated dose (MTD) and recommended phase II dose (RP2D) could not be determined in this study due to dose-limiting toxicity (DLT). No new safety signals were observed.

Section 5.2 'Pharmacokinetic properties' of the SmPC

Paediatric population

The pharmacokinetics of ribociclib were evaluated in paediatric (n=10) and young adult (n=2) patients with relapsed or refractory neuroblastoma or other solid tumours in the dose-finding part of a phase I/II study of Kisqali in combination with TOTEM as concurrent or sequential dosing (see section 5.1). The exposure of ribociclib increased with the dose increasing from 100 to 200 mg/m^2/day with T_{max} between 1 and 4 hours across patients. At the ribociclib dose of 100 mg/m^2/day with concurrent dosing of TOTEM, the geometric mean steady-state CL/F of ribociclib was 35.4 l/hr (69% CV) and the geometric mean accumulation ratio was 1.06 (53.9% CV) (n=5).

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

About the product

Ribociclib (Kisqali) is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6. These kinases are activated upon binding to D-cyclins and play a crucial role in signalling pathways which lead to cell cycle progression and cellular proliferation. The cyclin D-CDK4/6 complex regulates cell cycle progression through phosphorylation of the retinoblastoma protein (pRb).

Kisaqali was first approved in the EU on 22 August 2017 and is available as a 200 mg film-coated tablet for oral administration. The currently approved indications are:

Early breast cancer

Kisqali in combination with an aromatase inhibitor is indicated for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer at high risk of recurrence (see section 5.1 for selection criteria).

In pre- or perimenopausal women, or in men, the aromatase inhibitor should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

Advanced or metastatic breast cancer

Kisqali is indicated for the treatment of women with HR-positive, HER2-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy.

In pre- or perimenopausal women, the endocrine therapy should be combined with a LHRH agonist.

Background

Neuroblastoma (NB) is the third most common childhood malignancy. It is the most prevalent extracranial solid tumour in paediatric populations worldwide, representing 8-10% of childhood malignancies

High incidence of Cyclin D1 and CDK4 over-expression has been observed in NB cell lines. Besides NB, genetic alterations in the CDK4/6 pathway were seen in other paediatric solid tumours, including medulloblastoma (MB), high-grade glioma (HGG), malignant rhabdoid tumour (MRT), and rhabdomyosarcoma (RMS). It has been hypothesised that targeting cell cycle regulator CDK4/6 and the CCND1/CDK4 axis may provide therapeutic benefit for patients with relapsed or refractory high-risk NB or other solid tumours like MB, HGG, MRT, and RMS.

Ribociclib is one of a group of kinase inhibitors being explored for the treatment of NB and other solid tumours. Ribociclib monotherapy was previously studied in a Novartis-sponsored phase I Study (CLEE011X2102) in children and adolescents with r/r MRT, NB, and cyclin D-CDK4/6 pathway-activated tumours to determine the PK and safety of ribociclib in this population. Overall, ribociclib monotherapy was well tolerated in paediatric patients and the safety profile was comparable to that observed in adults. Based on the results from this study, 470 mg/m2/day was the maximum tolerated dose (MTD) and 350 mg/m2/day was the recommended dose for expansion (Geoerger et al, 2017). Apart from an abstract provided within the renewal procedure EMEA/H/C/004213/R/0034, this study has not been submitted to the EMA.

In addition, data from the Investigator Initiated Trial, AcSe-ESMART, in patients with advanced malignancies provided preliminary clinical experience of using ribociclib in combination with topotecan and temozolomide (TOTEM) for paediatric patients. The combination of ribociclib and TOTEM resulted

mainly in haematologic toxicity in the AcSe-ESMART trial, which mandated for the recommended phase 2 dose, a reduction to 75% of the ribociclib single-agent daily dose and 57% dose intensity and 66% of the TOTEM chemotherapy. Although there recommended phase 2 dose (RP2D) was determined in this study, no objective responses were observed.

Current application

Based on the previously available data in adult and paediatric populations with advanced cancer, and from preclinical models, a phase I/II interventional study CLEE011Q12101 (hereafter referred to as study Q12101) was designed to determine a safe dose and treatment schedule of ribociclib when combined with TOTEM, with an aim to provide a therapeutic opportunity for paediatric patients with high unmet medical need, especially those with relapsed or refractory high-risk NB.

Additionally, relapsed or refractory solid tumours other than NB were intended to be studied in phase I Part A and B, including Medulloblastoma (MB), High Grade Glioma (HGG), Malignant Rhabdoid Tumour (MRT), and Rhabdomyosarcoma (RMS), to be assessed for preliminary activity, and potentially for further evaluation if supported by the data generated from phase I.

The features of study Q12101, including design, study population, and endpoints were discussed with FDA, EMA and the PDCO (CHMP Scientific Advice, 2020; PIP EMEA-002765-PIP02-21; FDA Type C Meeting 2020, 2021, FDA Type D Meeting 2023).

This study was, however, prematurely terminated due to crossing a predetermined threshold for dose limiting toxicities (DLT) and poor tolerability with the study treatment combination across all cohorts eventually leading to the inability to determine the recommended phase 2 dose (RP2D) within the dose escalation phase (Phase I – part A).

With the current application, the study report for study Q12101 (Phase 1 – Part A) is submitted. The MAH has also provided a Clinical Overview and Clinical Summaries, summarising and discussing the data.

Phase I - Part A of study Q12101 is included in the Paediatric investigation plan (PIP) for ribociclib. With this submission, the MAH is fulfilling the Article 46 obligation for Study CLEE011Q12101.

The purpose of the current submission is to update the Product Information, reflecting the negative outcome of the paediatric study. The data do not support a paediatric indication and no changes to the indication are proposed.

Product information

The following updates of the Product information are proposed:

SmPC, Section 4.2

Paediatric population

The safety and efficacy of Kisqali in children and adolescents aged below 18 years have not been established. ***Currently available data on Kisqali in combination with topotecan and temozolomide (TOTEM) in paediatric patients are described in sections 5.1 and 5.2, but no recommendation on a posology can be made*** ~~*No data are available.*~~

SmPC, Section 5.1

Paediatric population

Study CLEE011Q12101

A phase I/II multicentre study was conducted to evaluate the efficacy and safety of the combination of ribociclib with TOTEM in paediatric (4 to <18 years, n=10) and young adult (18 to 20 years, n=2) patients with relapsed or refractory (r/r) neuroblastoma (NB) or other solid tumours. Three cohorts were completed in the phase I dose-finding part which investigated the following dose regimens in a 28-day treatment cycle: ribociclib 200 mg/m²/day (days 1 to 21) plus topotecan 0.75 mg/m²/day and temozolomide 150 mg/m²/day (days 1 to 5) (concurrent dosing); ribociclib 100 mg/m²/day (days 6 to 21) after topotecan 0.75 mg/m²/day and temozolomide 150 mg/m²/day (days 1 to 5) (sequential dosing); ribociclib 100 mg/m²/day (days 1 to 14) plus topotecan 0.75 mg/m²/day and temozolomide 100 mg/m²/day (days 1 to 5) (concurrent dosing). Patients had a median age of 14 years (n=12), 7 were female. No objective response was observed. The maximum tolerated dose (MTD) and recommended phase II dose (RP2D) could not be determined in this study. No new safety signals were observed.

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

SmPC, Section 5.2

Paediatric population

The pharmacokinetics of ribociclib were evaluated in paediatric (n=10) and young adult (n=2) patients with relapsed or refractory neuroblastoma or other solid tumours in the dose-finding part of a phase I/II study of Kisqali in combination with TOTEM as concurrent or sequential dosing (see section 5.1). The exposure of ribociclib increased with the dose increasing from 100 to 200 mg/m²/day with T_{max} between 1 and 4 hours across patients. At the ribociclib dose of 100 mg/m²/day with concurrent dosing of TOTEM, the geometric mean steady-state CL/F of ribociclib was 35.4 l/hr (69% CV) and the geometric mean accumulation ratio was 1.06 (53.9% CV) (n=5).

6. Clinical Pharmacology aspects

6.1. Methods – analysis of data submitted

Study CLEE011Q12101 (Study Q12101)

Study Q12101 was a phase I/II multicenter study to assess the efficacy and safety of ribociclib in combination with topotecan and temozolomide (TOTEM) in paediatric participants with relapsed or refractory NB and other solid tumours (including MB, HGG, MRT, and RMS). For a full description of the study design, see section 7 'Clinical Efficacy and Safety aspects'.

A secondary objective of the study was to characterize the pharmacokinetics (PK) of ribociclib in combination with topotecan and temozolimide during the dose finding phase (Phase I – part A).

Study population

The study was performed in 12 participants in three different cohorts as follows:

- Cohort A1 dose regimen: 2 participants (2 participants <18 years old), each participant experienced DLTs
- Cohort A2 dose regimen: 4 participants (3 participants <18 years old), 2 of 3 evaluable participants experienced DLTs
- Cohort A3 dose regimen: 6 participants (5 participants <18 years old), 2 of 6 evaluable participants experienced DLTs.

Out of the 12 participants enrolled, 10 were <18 years old.

Treatment

In the first dose finding level, ribociclib was intended to start at 200 mg/m^2/day p.o. daily on Days 1-21 concurrently in combination with TOTEM on Days 1-5 administered at a fixed standard dose.

- Cohort A1 evaluated participants with ribociclib at 200 mg/m2/day on Days 1-21 concurrently with topotecan-temozolomide 0.75 mg/m2/day i.v.-15 0mg/m2/day p.o. Days 1-5 in a 28-day cycle
- Cohort A2 evaluated participants with ribociclib at 100 mg/m2/day on Days 6-21 sequential to topotecan-temozolomide 0.75 mg/m2/day IV-150mg/m2/day p.o. Days 1-5 in a 28-day cycle.

Due to hematologic toxicities in the first two cohorts the protocol was amended to evaluate a modified TOTEM dose (topotecan at 0.75 mg/m^2/day i.v.; temozolomide at 100 mg/m^2/day p.o.) with a reduced number of ribociclib dosing days (from 21 to 14) as concurrent dosing.

After the protocol amendment the dose regimen for Cohort A3 was as follows:

- Cohort A3 dose regimen: concurrent dosing schedule with ribociclib Days 1-14 at a dose of 100 mg/m2/day in combination with temozolomide 100 mg/m2/day and topotecan 0.75 mg/m2/day Days 1-5, in a 28-day cycle.

Sampling schedule

Blood samples for PK purposes for the concurrent and sequential dosing were collected on day 1 cycle 1 at pre-dose, 1, 2, 4, 6, and 24 hours post dose, day 15 cycle 1 at pre-dose, 1, 2, 4, and 6 hours post dose, and on day 15 cycle 2 at pre-dose, 2, and 4 hours post dose.

Analysis

The concentrations of ribociclib and temozolomide were to be measured in human plasma, and topotecan as well as the active form of topotecan (topotecan lactone) in human blood were measured using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. The method validation and analytical performance were adequate. The method was capable of quantifying topotecan and topotecan lactone without any interference, and the entire sample storage period was covered by the validated long term storage stability.

6.2. Results

Study Q12101 measured the pharmacokinetics of ribociclib in paediatric patients. PK parameters were calculated following a single dose (C1D1 for cohort A1 and A3, C1D6 for cohort A2) as well as multiple-doses (C1D15 for cohort A2, C1D12 for cohort A3) administration of ribociclib. The PK analysis set included all participants who were included in the safety set i.e. all participants who received at least one dose of study treatment and who had at least one evaluable PK concentration. PK data were

limited in Cohort A1 (n=2 for C1D1, no steady-state data) and Cohort A2 (n=2 for steady-state data). Out of the 12 participants in the study, 10 were paediatric patients.

Following a single dose of 100 mg/m^2 ribociclib, the geometric mean of Cmax was 237 ng/mL and 312 ng/mL for Cohorts A2 and A3 respectively. The geometric mean of AUC0-24h was 2150 ng*h/mL and 3600 ng*h/mL for cohorts A2 and A3 respectively.

Following repeat dosing of 100 mg/m^2 ribociclib the geometric mean of steady-state Cmax was 211 ng/mL and 372 ng/mL for cohorts A2 and A3 respectively. The geometric mean of AUC0-24 was 2490 ng*h/mL and 4070 ng*h/mL for cohorts A2 and A3 respectively.

The exposure in Cohort A3 was slightly higher than the exposure in cohort A2 at the same dose level, with Cmax and AUC0-24 being 31.6% and 67.4% higher respectively after a single dose, and 76.3 % and 63.5% higher after at steady-state.

Following oral dosing of ribociclib in combination with TOTEM to paediatric and young adult patients, the exposure of ribociclib increased with the dose between 100 to 200 mg/m^2/day, and the Tmax was between 1 to 4 hours across dose levels. The accumulation ratio was small following repeat dosing for all participants (0.65-2.20). The geometric mean steady-state CL/F was 35.4 L/hr and the mean accumulation ratio was 1.06.

When comparing the PK exposure in study Q12101 with exposure in previous studies in paediatric and adult patients with advanced cancer it was found that the exposure in paediatric patients was generally comparable with that of earlier studies (study X2102) with Cmax and AUC being approximately 1.3 fold lower in study Q12101.

6.3. Discussion

Study Q12101 was a phase I/II study which included the secondary endpoint to assess the pharmacokinetics of ribociclib in combination with topotecan and temozolomide (TOTEM) in paediatric patients with relapsed or refractory (r/r) NB, MB, HGG, MRT, and RMS. Three different dosing regiments were explored.

The study was planned to include phase I – part A (dose finding), phase I – part B (multiple expansion cohorts at MTD/RP2D) and phase II (randomized placebo controlled). However, due to the DLTs observed in the phase I – Part A and the inability to identify the RP2D, the study was prematurely terminated after three cohorts had been treated in phase I – Part A.

Blood samples were taken after both single-dose and multiple dose to explore the exposure of ribociclib after both single-dose and at steady-state conditions. However, the bioanalytical report for the quantification of ribociclib concentrations could not be located. The applicant is requested to provide the bioanalytical report for the analysis of the samples from this study **(OC)**

The pharmacokinetics of ribociclib in the studied population has been explored and described, with exposure increasing with increasing dose levels, and the Tmax, accumulation ratio, and CL/F being described.

The MAH proposes updates to section 5.2 of the SmPC to describe the pharmacokinetics results of the study. The proposed updates are agreed.

7. Clinical Efficacy and Safety aspects

7.1. Methods – analysis of data submitted

Study CLEE011Q12101 (Study Q12101)

Study Q12101 was a phase I/II multicenter study to assess the efficacy and safety of ribociclib in combination with topotecan and temozolomide (TOTEM) in paediatric participants with relapsed or refractory NB and other solid tumours (including MB, HGG, MRT, and RMS).

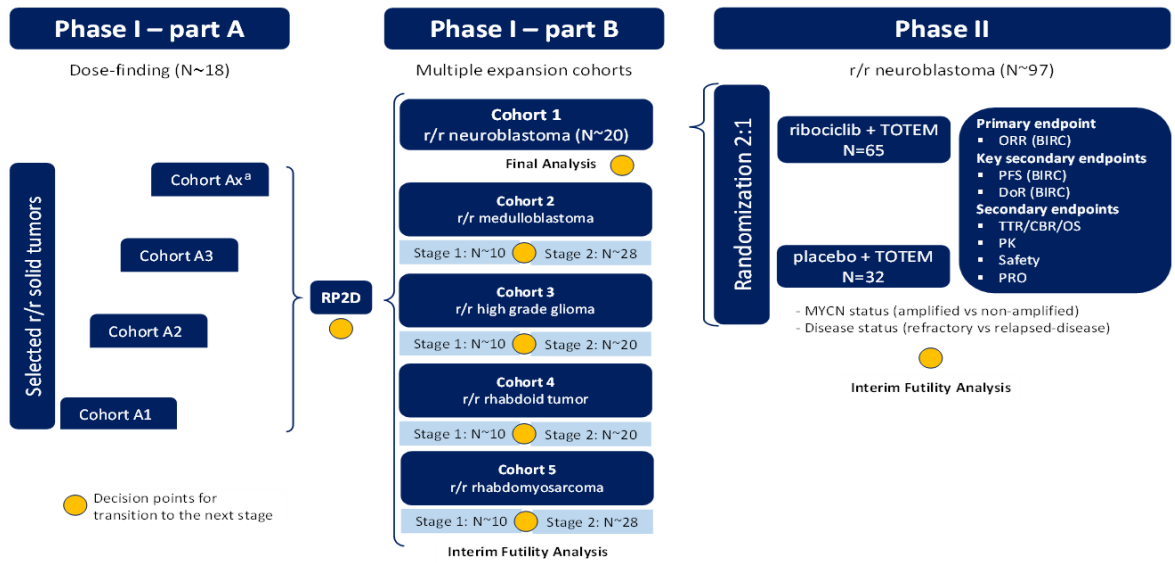
Primary objective

- to determine the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D) of ribociclib in combination with topotecan and temozolomide during the dose finding phase (Phase I – part A).

Secondary objectives

- to characterize the safety and tolerability of ribociclib in combination with topotecan and temozolomide
- to characterize the pharmacokinetics (PK) of ribociclib in combination with topotecan and temozolomide during the dose finding phase (Phase I – part A).

Study design (planned)



[a] Phase 1 – Part A: Cohort Ax where x indicates subsequent additional cohort(s) that would be explored depending on the outcome of the previous cohort.

After completion of Cohort A3 in phase I – Part A, the investigators, the Steering Committee members, and Novartis agreed to terminate the study due to the significant incidence of DLTs, poor tolerability observed in participants enrolled in phase I – part A, and the inability to identify the RP2D. Therefore, the study never reached phase I – part B, or phase II, and only phase 1 – Part A, is described in below.

Treatment

In the first dose finding level, ribociclib was intended to start at 200 mg/m2/day po daily on Days 1-21 concurrently in combination with TOTEM on Days 1-5 administered at a fixed standard dose. The dosing schedule was to continue until MTD or a suitable lower dose of ribociclib was identified as RP2D. Based on emerging PK and safety data from this study, a sequential dosing schedule of ribociclib on Days 6-21 in combination with fixed TOTEM dosing on Days 1-5 could be explored after concurrent dosing schedule was found intolerable.

Cohorts evaluated in phase I Part A: Prior to Protocol Amendment 2:

- Cohort A1 evaluated participants with ribociclib at 200 mg/m^2/day on Days 1-21 concurrently with TOTEM on Days 1-5 (topotecan 0.75 mg/m^2/day i.v. and temozolomide 150 mg/m^2/day p.o.), in a 28-day cycle
- Cohort A2 evaluated participants with ribociclib at 100 mg/m^2/day on Days 6-21 sequential to TOTEM on Days 1-5 (topotecan 0.75 mg/m^2/day i.v. and temozolomide 150 mg/m^2/day p.o.), in a 28-day cycle.

Due to observed high grade haematologic toxicities in the first 2 cohorts, the protocol was amended (Protocol Amendment 2 [08 March 2024]) to evaluate a modified TOTEM dose (topotecan at 0.75 mg/m^2/day i.v.; temozolomide at 100 mg/m^2/day p.o.) with a reduced number of ribociclib dosing days (from 21 to 14) as concurrent dosing. This regimen was chosen to mitigate the haematological toxicities and DLTs observed while allowing exposure to all treatment components for a sufficient duration throughout the cycle.

After Protocol Amendment 2, in phase I Part A, Cohort A3 was modified as:

- Cohort A3 dose regimen: concurrent dosing schedule with ribociclib Days 1-14 at a dose of 100 mg/m^2/day in combination with TOTEM on Days 1-5 (topotecan 0.75 mg/m^2/day i.v. and temozolomide 100 mg/m^2/day p.o.), in a 28-day cycle.

Study subjects

Approximately 18 participants (age > 12 months to < 21 years) were planned to be enrolled in phase 1 Part A of the study, however only 12 participants were enrolled into cohorts due to the observed incidence of DLTs within each cohort. Of the 12 participants enrolled, 10 participants were 4 to 18 years old.

- Cohort A1 dose regimen: 2 participants (all <18 years old), each participant experienced DLTs
- Cohort A2 dose regimen: 4 participants (3 participants <18 years old), 2 of 3 evaluable participants experienced DLTs
- Cohort A3 dose regimen: 6 participants (5 participants <18 years old), 2 of 6 evaluable participants experienced DLTs.

Endpoints

The primary endpoint of phase 1 – part A was the incidence of DLTs during the Cycle 1 of each dose level associated with administration of ribociclib in combination with TOTEM. The study utilized a Bayesian Hierarchical Logistic Regression Model (BHLRM) to identify MTD. The adaptive BHLRM was guided by the Escalate with Overdose Control (EWOC) principle to control the risk of DLT in future participants on study. This method was more likely to assign fewer participants to either sub-therapeutic or severely toxic dose levels and estimate the MTD with smaller average bias and error than the up-and-down methods such as 3+3.

All efficacy endpoints were exploratory in nature. The efficacy endpoints included:

- objective response rate (ORR; percentage of participants with a confirmed best overall of complete response [CR] or partial response [PR])
- duration or response (DOR)
- progression-free survival (PFS)
- time to response (TTR).

Tumour response was assessed by local Investigator. Different evaluation criteria were recommended across indications:

- NB was assessed according to International Neuroblastoma Response Criteria (INRC)
- MB, MRT and RMS were assessed based on Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1.
- HGG was assessed according to Response Assessment in Neuro-Oncology (RANO).

Analysis set

All 12 enrolled participants were included in the Full analysis set, Safety set and the Pharmacokinetic analysis set. All participants except one were included in the Dose determining set as the participant discontinued in Cohort A2 due to subject decision after one dose of ribociclib.

7.2. Results

Study population

Table 1. Study population – Demographics and diagnosis

Cohort	Participant	Age (years)	Sex	Diagnosis
Cohort A1	001	[4-20]	[***]	NB
	002	[4-20]	[***]	HGG (Glioblastoma)
Cohort A2	003	[4-20]	[***]	Alveolar RMS
	004	[4-20]	[***]	MB
	005	[4-20]	[***]	HGG (Astrocytoma malignant)
	006	[4-20]	[***]	NB
Cohort A3	007	[4-20]	[***]	HGG (Malignant glioma)
	008	[4-20]	[***]	HGG (Malignant glioma)
	009	[4-20]	[***]	RMS
	010	[4-20]	[***]	Alveolar RMS
	011	[4-20]	[***]	Alveolar RMS
	012	[4-20]	[***]	Alveolar RMS

HGG = high-grade glioma; MB = medulloblastoma; NB = neuroblastoma; RMS = rhabdomyosarcoma.

7.2.1. Efficacy

ORR:

No objective response was observed across all cohorts (Table 2).

- A total of 6 participants with RMS or MB were assessed based on RECIST. The BOR for 2/6 or these participants was stable disease, for 2/6 participants was progressive disease and for 2/6 participants was non-evaluable.
- A total of 4 participants with HGG were assessed based on RANO. The BOR for one participant was stable disease. The remaining 3 participants had progressive disease.
- Only two participants with NB were enrolled and assessed by INRC. No responses were observed and both participants developed progressive disease at end of treatment.

Table 2. Best overall response per RECIST 1.1 and overall Response Rate (ORR) based on investigator/radiology review

	RIBO 100 mg/m2 D6 - D21 + TOPO 0.75 mg/m2 + TEMO 150 mg/m2 N = 2 n (%)	**RIBO 100 mg/m2 D1 - D14 + TOPO 0.75 mg/m2 + TEMO 100 mg/m2 N = 4 n (%)**
Best overall response		
Complete Response (CR)	0	0
Partial Response (PR)	0	0
Stable Disease (SD)	1 (50.0)	1 (25.0)
Progressive Disease (PD)	0	2 (50.0)
Non-CR/Non-PD (NCRNPD)	0	0
Non-Evaluable (NE)	1 (50.0)	1 (25.0)
Overall Response Rate (ORR: CR+PR)	0	0
Disease Control Rate (DCR: CR+PR+SD)	1 (50.0)	1 (25.0)
Clinical Benefit Rate (CBR: CR+PR+SD+Non-CR/Non-PD >=24 weeks)	0	0

- N is the denominator for percentage calculation. n is number of subjects in the corresponding category.
- ORR = proportion of subjects with confirmed CR or PR.
- DCR = Proportion of patients with confirmed CR or PR or SD.
- CBR = proportion of patients with confirmed CR or PR, or (SD or Non-CR/Non-PD>=24 weeks).

PFS

- Per RECIST: A total of five participants with RMS and one participant with MB were assessed for PFS per RECIST. The PFS was non-evaluable for two participants. Three participants had disease progression and one participant died.
- Per RANO: A total of four participants with HGG were assessed for PFS based on RANO. All four participants had events of disease progression.
- INRC review: Only two participants with NB were enrolled in Phase 1 Part A of the study. No responses were observed. Both participants developed progressive disease at end of treatment.

DOR and TTR:

- not evaluable due to no responses.

Overall, no efficacy was observed in this population and despite 2 young adults participants included in the FAS, overall conclusion is the same in the paediatric population (4 to 18 years).

7.2.2. Safety

Safety was assessed based on all treated participants; toxicities were defined by CTCAE (version 5.0). Incidence and severity of adverse events (AEs), causality attribution to drug, time to event onset, duration of the event, its resolution and concomitant medications administered were recorded. AEs were collected for each participant until 30 days after the last trial drug was administered (ribociclib and/or TOTEM).

Exposure

The planned treatment per 28-day cycle in the three cohorts was:

- Cohort A1: ribociclib 200 mg/m^2/day D1-D21 + topotecan 0.75 mg/m^2/day D1-D5 + temozolomide 150 mg/m^2/day D1-D5
- Cohort A2: ribociclib 100 mg/m^2/day D6-D21 + topotecan 0.75 mg/m^2/day D1-D5 + temozolomide 150 mg/m^2/day D1-D5
- Cohort A3: ribociclib 100 mg/m^2/day D1-D14 + topotecan 0.75 mg/m^2/day D1-D5 + temozolomide 100 mg/m^2/day D1-D5.

Exposure to study treatment is described in Table 3 below.

In summary:

- In Cohort A1, the median exposure of participants to ribociclib was 3.6 months and the median exposure to both topotecan and temozolomide was 3.3 months.
- In Cohort A2, the median exposure of participants to ribociclib was 0.9 months and the median exposure to both topotecan and temozolomide was 0.6 months.
- In Cohort A3, the median exposure of participants to ribociclib was 1.3 months and the median exposure to both topotecan and temozolomide was 1.1 months

Table 3. Duration of exposure to study treatment (Safety set)

Study treatment and Ribociclib

	Study treatment			Ribociclib		
Duration of exposure	**RIBO 200 mg/m2 D1 - D21 + TOPO 0.75 mg/m2 + TEMO 150 mg/m2 N = 2**	**RIBO 100 mg/m2 D6 - D21 + TOPO 0.75 mg/m2 + TEMO 150 mg/m2 N = 4**	**RIBO 100 mg/m2 D1 - D14 + TOPO 0.75 mg/m2 + TEMO 100 mg/m2 N = 6**	**RIBO 200 mg/m2 D1 - D21 + TOPO 0.75 mg/m2 + TEMO 150 mg/m2 N = 2**	**RIBO 100 mg/m2 D6 - D21 + TOPO 0.75 mg/m2 + TEMO 150 mg/m2 N = 4**	**RIBO 100 mg/m2 D1 - D14 + TOPO 0.75 mg/m2 + TEMO 100 mg/m2 N = 6**
Total number of subjects received component-n (%)	2 (100)	4 (100)	6 (100)	2 (100)	4 (100)	6 (100)
Duration of exposure (months)						
Mean	3.6	1.3	1.4	3.6	1.1	1.4
SD	2.60	1.17	1.06	2.60	1.17	1.06
Median	3.6	1.1	1.3	3.6	0.9	1.3
Minimum	1.8	0.2	0.3	1.8	0.0	0.3
Maximum	5.5	2.8	3.2	5.5	2.6	3.2
Exposure categories (months)-n (%)						
<1	0	2 (50.0)	2 (33.3)	0	2 (50.0)	2 (33.3)
≥1	1 (50.0)	1 (25.0)	3 (50.0)	1 (50.0)	1 (25.0)	3 (50.0)
≥2	0	1 (25.0)	0	0	1 (25.0)	0
≥3	0	0	1 (16.7)	0	0	1 (16.7)
≥4	1 (50.0)	0	0	1 (50.0)	0	0

Overview of Dose limiting toxicities (DLTs)

Overall, across all treatment cohorts (n=12) in phase I part A, 6 participants had DLTs (2 in each cohort) of which 4 participants had DLTs consisting of AEs during the first cycle of study treatment. A total of 5 participants had less than 75% of the planned dose in the first cycle due to toxicity (relative dose intensity DLT) (Table 4).

Table 4. DLT evaluations for all participants

Cohort	Participant No. Age (years)/Sex/Diagnosis	No. of days treated with ribociclib in Cycle 1	DLTs
Cohort A1	001 [4-20]/ [***]/NB	10 days	G4 neutropenia (Day 20, lasting 9 days); received <75% of the planned dose in the first cycle due to toxicity
	002 [4-20] / [***] HGG	10 days	G4 neutropenia (Day 13, lasting 9 days); received <75% of the planned dose in the first cycle due to toxicity
Cohort A2	003 [4-20] / [***] /Alveolar RMS	16 days	None
	004 [4-20] / [***] /MB	1 day	Not evaluable for DLT
	005 [4-20] / [***] /Anaplastic astrocytoma	8 days	G4 neutropenia (Day 13, lasting 9 days); received <75% of the planned dose in the first cycle due to toxicity
	006 [4-20] / [***] /NB	10 days	Received <75% of the planned dose in the first cycle due to toxicity (grade 2 ventricular tachycardia)
Cohort A3	007 [4-20] / [***] /HGG	14 days	None
	008 [4-20] [***] /HGG	14 days	None
	009 [4-20] / [***] /RMS	10 days	Grade 3 device-related infection and grade 3 anemia; received <75% of the planned dose in the first cycle due to toxicity
	010 [4-20] / [***] /Alveolar RMS	14 days	None
	011 [4-20] / [***] /Alveolar RMS	14 days	None
	012 [4-20] / [***] /Alveolar RMS	14 days	Grade 3 hypoxia, grade 4 dyspnea, grade 3 hypotension, grade 5 respiratory failure

HGG = high-grade glioma; MB = medulloblastoma; NB = neuroblastoma; RMS = rhabdomyosarcoma.

- **Cohort A1:** Two participants reported both haematology (grade 4 neutropenia lasting more than 7 consecutive days within the dose determining period) and relative dose intensity DLTs of receiving less than 75% of planned dose in the first cycle due to these haematology toxicities.
- **Cohort A2:** Two participants reported relative dose intensity DLTs of receiving less than 75% of planned dose in the first cycle for toxicity reasons and one of the participants also reported haematology DLT with grade 4 neutropenia lasting more than 7 consecutive days within the dose determining period.

- **Cohort A3:** One participant reported the relative dose intensity DLT of receiving less than 75% of planned dose in the first cycle due to grade 3 device-related infection and grade 3 anemia. Another participant reported SAEs of grade 3 hypoxia, grade 4 dyspnea, grade 3 hypotension, and grade 5 respiratory failure with a fatal outcome, all of which met the non-haematological DLTs.

The MTD/RP2D was not identified based on the review of the overall safety profile observed during the study conduct, as well as the results of the statistical BHLRM and the available PK, PD and preliminary efficacy data. The BHLRM models estimated an excessive toxicity of ribociclib in combination with topotecan and temozolomide i.e. Prob[DLT>33%|data] higher than 25% which exceeded the limits allowed by the protocol.

Adverse events

An overview of deaths and adverse events is provided in Table 5.

Table 5. Summary of death and adverse events (Safety set)

Category	RIBO 200 mg/m2 D1 - D21 + TOPO 0.75 mg/m2 + TEMO 150 mg/m2 N = 2 n (%)	RIBO 100 mg/m2 D6 - D21 + TOPO 0.75 mg/m2 + TEMO 150 mg/m2 N = 4 n (%)	RIBO 100 mg/m2 D1 - D14 + TOPO 0.75 mg/m2 + TEMO 100 mg/m2 N = 6 n (%)	All patients N = 12 n (%)
All deaths [1]	0	0	2 (33.3)	2 (16.7)
On-treatment deaths [2]	0	0	1 (16.7)	1 (8.3)
Adverse events	2 (100)	4 (100)	6 (100)	12 (100)
Suspected to be drug-related	2 (100)	4 (100)	6 (100)	12 (100)
Serious adverse events	2 (100)	0	4 (66.7)	6 (50.0)
Suspected to be drug-related	0	0	3 (50.0)	3 (25.0)
AEs leading to discontinuation	0	1 (25.0)	0	1 (8.3)
Suspected to be drug-related	0	1 (25.0)	0	1 (8.3)
AEs requiring dose interruption	2 (100)	3 (75.0)	3 (50.0)	8 (66.7)
Suspected to be drug-related	2 (100)	3 (75.0)	2 (33.3)	7 (58.3)
AEs requiring dose adjustment	2 (100)	2 (50.0)	0	4 (33.3)
Suspected to be drug-related	2 (100)	2 (50.0)	0	4 (33.3)
AEs requiring additional therapy	2 (100)	4 (100)	6 (100)	12 (100)
Suspected to be drug-related	2 (100)	4 (100)	5 (83.3)	11 (91.7)
AEs of special interest	2 (100)	4 (100)	6 (100)	12 (100)
Suspected to be drug-related	2 (100)	4 (100)	6 (100)	12 (100)

1. All deaths including those >30 days after last date of study treatment.
2. Deaths occurring >30 days after last date of study treatment are not included.
- Suspected to be drug related refers to any component of study treatment.
- Additional therapy includes all non-drug therapy and concomitant medications.
- Discontinuation refers to discontinuation of any treatment component.
- AEs up to 30 days after the last date of study treatment are included.
- MedDRA version 27.1, CTCAE v5.0.

Common Adverse events

All 12 participants (100%) had at least one AE in phase I Part A of the study. Overall, the most frequently reported (>50% of all participants) AEs by SOC were Blood and lymphatic systems disorders and Gastrointestinal disorders (100%), General disorders and administration site conditions (66.7%), Investigations (58.3%), and Nervous system disorders (58.3%).

The most commonly reported (≥ 50% of all participants) AEs by PT in all cohorts were anaemia (91.7%), nausea (83.3%), vomiting (75.0%), headache, neutrophil count decreased, platelet count decreased, thrombocytopenia, and white blood cell count decreased (50.0% each).

The most frequently reported (≥50% of all participants) AEs by PT suspected to be treatment related were anaemia (91.7%), nausea (83.3%), vomiting (58.3%), neutrophil count decreased, platelet count decreased, thrombocytopenia, and white blood cell count decreased (50.0% each). Most of these AEs were haematological in nature.

Overall, across all cohort groups in phase I Part A, 2/12 participants (16.7%) reported AEs of grade 3, 8/12 participants (66.7%) reported AEs of maximum grade 4 and 1/12 participant (8.3%) reported an AE of maximum grade 5.

Deaths

A total of 2 deaths were reported. Of these, one was on-treatment death due to treatment-related SAE (PT: respiratory failure). The second death was due to the underlying disease and occurred outside of the treatment window i.e. 31 days after the last study treatment).

Adverse events of special interest

Table 6. Overview of adverse events of special interest, irrespective of causality, by grouping

Risk or adverse reaction names	RIBO 200 mg/m2 D1 - D21 + TOPO 0.75 mg/m2 + TEMO 150 mg/m2 N=2 n (%)	RIBO 100 mg/m2 D6 - D21 + TOPO 0.75 mg/m2 + TEMO 150 mg/m2 N=4 n (%)	RIBO 100 mg/m2 D1 - D14 + TOPO 0.75 mg/m2 + TEMO 100 mg/m2 N=6 n (%)	All patients N=12 n (%)
-Any risk or adverse reaction names	2 (100)	4 (100)	6 (100)	12 (100)
Hepatobiliary toxicity	0	2 (50.0)	3 (50.0)	5 (41.7)
Myelosuppression - Anaemia	2 (100)	3 (75.0)	6 (100)	11 (91.7)
Myelosuppression - Infections	2 (100)	0	2 (33.3)	4 (33.3)
Myelosuppression - Leukopenia	2 (100)	3 (75.0)	6 (100)	11 (91.7)
Myelosuppression - Neutropenia	2 (100)	3 (75.0)	6 (100)	11 (91.7)
Myelosuppression - Thrombocytopenia	2 (100)	4 (100)	6 (100)	12 (100)
QT interval prolongation	0	1 (25.0)	0	1 (8.3)
Renal toxicity	0	1 (25.0)	1 (16.7)	2 (16.7)

-Patients with multiple events in a grouping are counted only once in the grouping.
-AESI grouping terms are presented alphabetically.
-QT interval prolongation AESI grouping included arrhythmias therefore ventricular tachycardia from patient in second cohort was included. No ECG QT prolonged events were reported in the study.
-MedDRA version 27.1, CTCAE v5.0.

Treatment discontinuations and dose modifications

One participant from the Cohort A2 had an AE which led to discontinuation (PT: ventricular tachycardia).

Four participants (33.3%) across all three cohorts had AEs which resulted in dose adjustments. Two participants, each in Cohort A1 (PT: neutropenia, anaemia, leukopenia, thrombocytopenia) and Cohort A2 (PT: neutropenia, neutrophil count decreased) had AEs which required dose adjustments due to high grade haematologic events. There were no dose adjustments in Cohort A3.

Eight participants (66.7%) across all three cohorts had AEs that required dose interruptions. Two participants in Cohort A1 (PT: leukopenia, neutropenia and thrombocytopenia), three participants each in Cohort A2 (PT: neutropenia, sinus tachycardia, platelet count decreased and white blood cell count decreased) and Cohort A3 had (PT: anaemia, febrile neutropenia, device related infection, contusion, fall and platelet count decreased) AEs which lead to dose interruption.

Palatability

A majority (N=11) of the participants indicated in the palatability questionnaire that the ribociclib oral solution tasted bad to very bad and one participant indicated that the oral solution tasted good.

MAH's overall summary of safety results

Two participants in Cohort A3 died in the duration of the trial of which one was an on-treatment death (PT: respiratory failure).

Overall, the most frequently reported (≥50% of all participants) AEs by PT were anaemia (11 participants; 91.7%), nausea (10 participants; 83.3%), vomiting (9 participants; 75.0%), headache (6 participants; 50.0%), neutrophil count decreased (6 participants; 50.0%), platelet count decreased (6

participants; 50.0%), thrombocytopenia (6 participants; 50.0%) and white blood cell count decreased (6 participants; 50.0%).

Overall, SAEs were observed in 6 participants (50.0%) across all cohorts. One participant had a grade 5 SAE (respiratory failure) in Cohort A3.

7.3. Discussion

Study Q12101 was a phase I/II study to assess the efficacy and safety of ribociclib in combination with topotecan and temozolomide (TOTEM) in paediatric patients with relapsed or refractory (r/r) NB, MB, HGG, MRT, and RMS. Three different dosing regiments were explored.

The primary objective of the study was to determine the MTD and/or the RP2D.

The study was planned to include phase I – part A (dose finding), phase I – part B (multiple expansion cohorts at MTD/RP2D) and phase II (randomized placebo controlled). However, due to the DLTs observed in the phase I – Part A and the inability to identify the RP2D, the study was prematurely terminated after three cohorts had been treated in phase I – Part A.

A total of 12 participants were enrolled. At initial diagnosis, the majority (N=10) had stage IV cancer. Of the 12, two participants had relapsed or refractory neuroblastoma at the study entry.

For ORR, there were no responders.

For PFS, the two patient with NB had no response and progressive disease at end of treatment. Among the remaining 10 participants, 7 participants had progression and one participant died. Two patients were non-evaluable.

No new safety signals were identified during the conduct of the trial. The most commonly reported AEs were haematological and gastrointestinal toxicities, as anticipated with the combination treatment, ribociclib and TOTEM. There were two deaths of which one occurred on-treatment and was suspected to be study treatment related (Grade 5 respiratory failure) and one was due to indication.

The combination of treatment of ribociclib with TOTEM was, thus, concluded to be intolerable, leading to DLTs in 6 participants (2 per cohort) and high grade haematological AEs in majority of the participants.

With the three different dosing regimens studied, all possible provisional doses and schedules of ribociclib were considered explored. The MAH concluded that the overall study results did not support any further investigation of this treatment combination in paediatric and young adult patients with relapsed/refractory solid tumours, including neuroblastoma. In line with the stopping rule outlined in the protocol, the Sponsor terminated the study and no additional subjects were enrolled.

Therefore, the MAH suggests that the data generated does not support the intended paediatric indication *"treatment of relapsed or refractory NB in patients aged 12 months and above in combination with temozolomide and topotecan"* as stated in the PIP.

This conclusion is agreed and the PIP can be considered completed in terms of Clinical Study 3.

The MAH proposes updates to sections 4.2 and 5.1 of the SmPC to describe the efficacy/safety results of the study. The proposed updates are agreed.

The Package Leaflet (PL) is not updated, which is considered adequate.

8. Changes to the Product Information

As a result of this variation, sections 4.2, 5.1 and 5.2 of the SmPC are being updated to reflect the results of study Q12101. The Package Leaflet (PL) is not updated.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

9. Request for supplementary information

9.1. Major objections

N/A

9.2. Other concerns

1. A bioanalytical report for the quantification of ribociclib concentrations could not be located. The applicant is requested to provide the bioanalytical report for the analysis of the samples from this study.

10. Assessment of the responses to the request for supplementary information

10.1. Other concerns

Clinical aspects

Question 1.

A bioanalytical report for the quantification of ribociclib concentrations could not be located. The applicant is requested to provide the bioanalytical report for the analysis of the samples from this study.

Summary of the MAH's response

Novartis is hereby providing the Bioanalytical data report: "Determination of LEE011 in K3EDTA human plasma" and the corresponding Method validation report in module 5.3.5.4 Other Study Reports.

Assessment of the MAH's response

The bioanalytical report has been provided and is considered adequate.

Issue resolved

Product information aspects

Comment:

With the current application the MAH suggests updates to the SmPC to reflect the results of study CLEE011Q12101. No updates are proposed for the PL. The proposed updates are agreed, but some additions are suggested in Section 5.1.

Summary of the MAH's response

Novartis acknowledges the proposal from CHMP rapporteur in the annotated Product information and agrees to modify the text in SmPC Section 5.1 with one minor editorial change.

Assessment of the MAH's response

The SmPC has been adequately updated.

Issue resolved

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance.