Amsterdam, 23 April 2026
EMADOC-1700519818-2891601
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Ibrance

International non-proprietary name: palbociclib

Procedure no.: EMA/PAM/0000327049

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	**Description**	**Planned date**	**Actual Date**
☐	CHMP Rapporteur AR	30 March 2026	30 March 2026
☐	CHMP comments	13 April 2026	N/A
☐	Updated CHMP Rapporteur AR	16 April 2026	N/A
☒	CHMP outcome	23 April 2026	23 April 2026

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1. Introduction

On 4 February 2026, the MAH submitted a completed paediatric study: study A5481092 for IBRANCE, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH has submitted the final data of study A5481092.

The 1st and 2nd interim reports of this study were previously assessed within the procedures EMEA/H/C/003853/P46/006 and EMA/PAM/0000250384 (P46), respectively.

The MAH stated that study A5481092 is the clinical measure of the agreed palbociclib paediatric investigational plan (PIP) in the treatment of Ewing sarcoma (EWS) P/0117/2022.

An update of the Product Information to include the results of all the measures agreed in the palbociclib PIP in recurrent or refractory (r/r) EWS P/0117/2022 was made in the Type II variation, EMEA/H/C/003853/ II/0045.

The MAH does not consider that any further changes in the palbociclib Product Information are warranted at this stage.

2.2. Information on the pharmaceutical formulation used in the study

Palbociclib was administered either as capsule or oral solution (concentration 25 mg/ml).

2.3. Clinical aspects

2.3.1. Introduction

This is the 3rd and final report of study A5481092 and presents the final data based on the data cut-off date of 06 August 2025 (Last Patient Last Visit (LPLV)).

Study A5481092 is a phase 1/2, multicentre, open label study evaluating palbociclib in combination with either irinotecan (IRN) and temozolomide (TMZ, or topotecan (TOPO) and cyclophosphamide (CTX), in paediatric patients with relapsed/refractory (r/r) solid tumours. The study included a non-randomized phase 1 part for r/r solid tumours, followed by potential non-randomized Tumour Specific Cohorts (TSCs), and a randomized phase 2 part for r/r EWS.

The 1st interim analysis (cut-off date: 31 July 2023) was performed when the pre-specified target number of event-free survival (EFS) events had been reached and covered both phase 1 (excluding TSC) and phase 2. The results did not show an improved EFS by adding palbociclib to the combination of IRN and TMZ. On the contrary, palbociclib appeared to have a detrimental effect on EFS as compared with IRN+TMZ alone in this patient population. Thus, the study crossed the pre-specified futility boundary at the first pre-planned interim analysis. The MAH's decision to stop enrolment was supported.

The 2nd interim analysis (cut-off date: 26 August 2024) was performed after the last participant enrolled in the Neuroblastoma (NB) TSC had received treatment with palbociclib in combination with TOPO + CTX for six months. The NB TSC results did not meet the pre-specified statistical criteria to proceed whereby enrolment to Stage 2 NB TSC was terminated.

Thus, no patients have been enrolled to study A5481092 since the last report. The results presented in this 3rd report are:

- Final efficacy and safety data from the Neuroblastoma TSC
- Final OS data (cut-off date: 06 August 2025) from phase 1 and phase 2.

2.3.2. Clinical study A5481092

2.3.2.1. Description

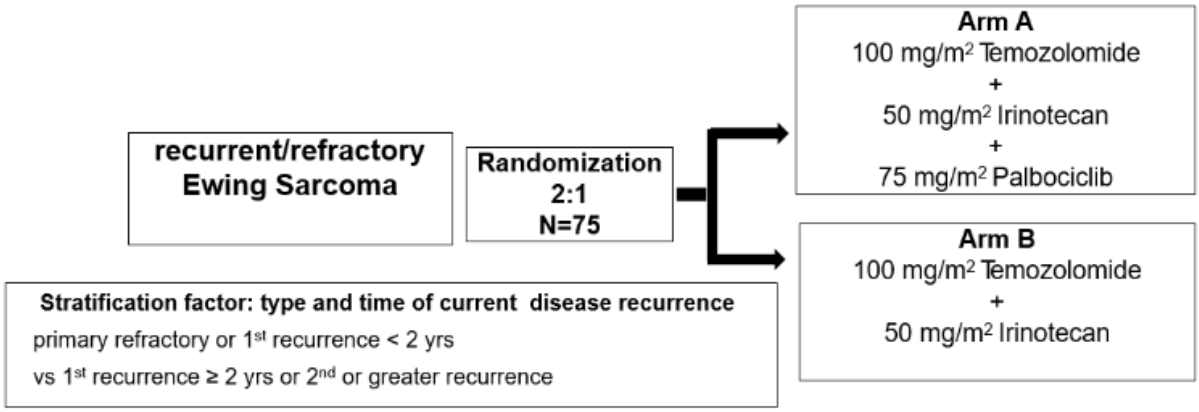
Study A5481092 is a phase 1/2 multicentre, open-label study to evaluate palbociclib in combination with chemotherapy in children, adolescents and young adults (aged ≥2 and <21 years at the time of study entry) with r/r solid tumours.

The study consists of a non-randomized dose-escalating phase 1 part for participants with r/r solid tumours followed by potential tumour specific cohorts (TSCs) and a randomized phase 2 part for participants with r/r Ewing sarcoma (EWS). The phase 2 portion is part of the agreed PIP for palbociclib in the treatment of EFS.

The dose-escalating phase 1 part of the study, evaluated five doses of palbociclib (40, 55, 75, 95 and 115 mg/m^2) in order to identify the recommended dose for phase 2, while the randomized phase 2 part of the study compared the efficacy of palbociclib (75 mg/m^2) in combination with IRN and TMZ versus IRN and TMZ alone in children, adolescents, and young adults with r/r EWS for whom no standard therapy was available (see Figure 1).

If 2 or more patients from dose escalation / dose determination part and / or dose expansion cohorts showed a confirmed objective response in a specific tumour type (e.g. neuroblastoma, rhabdomyosarcoma, rhabdoid tumour or medulloblastoma, etc), a TSC with a maximum of 21 patients per cohort was to be initiated to further evaluate antitumor activity of palbociclib in combination with IRN and TMZ or TOPO and CTX in each specific tumour type using a modified Simon's 2-stage optimal design.

Figure 1. Study Scheme – Phase 2 Palbociclib in Combination with IRN and TMZ in Ewing sarcoma (EWS)



2.3.2.2. Objectives and endpoints

	Primary objectives	**Endpoints**
Dose escalation/dose determination parts	To estimate the MTD for the combination of palbociclib, TMZ and IRN in children, adolescents, and young adults with r/r solid tumours. To determine the potential RP2D for palbociclib in combination with TOPO and CTX in children, adolescents, and young adults with r/r solid tumours	First cycle DLTs
Dose expansion cohort	To evaluate the safety, and confirm the RP2D for the combination of palbociclib, TMZ, and IRN at the MTD in children, adolescents and young adults with r/r solid tumours that are known to be sensitive to a CDK4/6 inhibitor. To evaluate the safety, and confirm the RP2D for the combination palbociclib CTX, and TOPO in children, adolescents and young adults with r/r solid tumours that are known to be sensitive to a CDK4/6 inhibitor.	AEs as characterized by type, frequency, severity, timing, seriousness, and relationship to study therapy; laboratory test data including HbA1c as characterized by type, frequency, severity, and timing; ECG parameters, and vital signs
	To evaluate the preliminary antitumor activity of palbociclib combined with TMZ and IRN. To evaluate the preliminary antitumor activity of palbociclib combined with TOPO and CTX	OR, as assessed by investigator using RECIST version 1.1/modified RANO for CNS malignancies/INRC for neuroblastoma
Randomised Phase 2	To compare the efficacy of palbociclib in combination with TMZ and IRN vs TMZ and IRN chemotherapy alone in the treatment of children, adolescents, and young adults with r/r EWS	EFS based on investigator assessment

Abbreviations: AEs, adverse events; DLT, dose limiting toxicity, EFS, event-free survival; OR, objective response

2.3.2.3. Study participants

A total of 128 participants (aged ≥2 and <21 years at the time of study entry) with r/r solid tumours were enrolled at 110 centres in 19 countries.

As of the LPLV (06 August 2025):

Phase 1

A total of 59 participants were treated in the dose-escalating phase 1 part of the study.

- Thirty-two (32) participants were treated with the combination of palbociclib + IRN + TMZ. All treated participants discontinued the study intervention with the most common reason being progressive disease. A total of 27 participants (81.8%) entered the follow-up period, of which 22 participants (66.7%) discontinued with the most common reason being death. Five (5) participants (15.2%) completed the follow-up period.
- Twenty-six (26) participants were treated with the combination of palbociclib + TOPO + CTX. A total of 25 participants (96.2%) discontinued the study intervention with the most common reason being progressive disease. A total of 23 participants (88.5%) entered the follow-up period, of which 21 participants (80.8%) discontinued with the most common reason being death. Two (2) participants (7.7%) who completed the follow-up period.

Phase 2

A total of 62 participants were treated in the expanded Phase 2 part of the study.

- Forty-two (42) participants were treated with the combination of palbociclib + IRN + TMZ (palbociclib arm). All treated participants (100.0%) discontinued the study intervention with the most common reason being progressive disease. A total of 37 participants (88.1%) entered the follow-up period, of which 33 participants (78.6%) discontinued with the most common reason being death. Four (4) participants completed the follow-up period.
- Twenty-one (21) participants were treated with the combination of IRN + TMZ (control arm). A total of 21 participants (100.0%) entered the follow-up period, of which 20 participants (95.2%) discontinued with the most common reason being death. One (1) participant completed the follow-up period.

TSC

- Two (2) participants with r/r neuroblastoma (NB) from phase 1 dose determination part and dose expansion cohort treated with palbociclib plus TOPO and CTX showed the confirmed objective responses. Therefore, per protocol a non-randomized TSC for NB was opened, including additional 5 participants enrolled in Stage 1.
- Six (6) of 7 treated participants (85.7%) in Stage 1 discontinued the treatment due to withdrawal by parent/guardian (n=2), progressive diseases (n=3), and other (n=1). One participant (14.3%) completed the treatment phase. All 7 participants (100.0%) entered the follow-up period, 4 participants (57.1%) discontinued the study due to withdrawal by subject (n=1), death (n=2), study terminated by sponsor (n=1). Three (3) participants (42.9%) completed the follow-up period.
- The NB TSC interim results (cut-off date: 26 August 2024) did not meet the pre-specified statistical criteria to proceed and therefore enrolment to Stage 2 NB TSC was terminated.

2.3.2.4. Demographics

Phase 1

For further details, refer to the 1st interim report assessed within the procedure EMEA/H/C/003853/P46/006.

Phase 2

For further details, refer to the 2nd interim report assessed within the procedure EMA/PAM/0000250384 (P46).

The demographics in the phase 2 part of the study were in general well balanced between treatment arms. The median age was 13.5 years (range: 5, 19) in the palbociclib arm and 15.0 years (range: 6, 20) years in the control arm, with most participants aged <18 years old in both arms (85.7% versus 85.7%). Type and time of current disease recurrence were balanced between the two arms (both 71.4% of participants had primary refractory or first recurrence <2 years and both 28.6% of participants had first recurrence ≥2 years or second or greater recurrence). The majority of participants had metastatic recurrence in both arms (81.0% versus 85.7%) and most had measurable disease (76.2% versus 95.2%).

TSC

For further details, refer to the 2nd interim report assessed within the procedure EMA/PAM/0000250384 (P46).

2.3.2.5. Efficacy results

Most results are presented in the 1st and 2nd interim reports assessed within the procedures EMEA/H/C/003853/P46/006 and EMA/PAM/0000250384 (P46).

Phase 1

Overall survival (LPLV; data cut-off 06 August 2025)

Palbociclib + IRN + TMZ: The median OS was 13.04 months (95% CI: 4.67, 25.30) in Dose Expansion cohort and 13.04 months (95% CI: 5.78, 25.30) in the pooled Dose Level 2 (DL2) and Dose Expansion cohort.

Palbociclib + TOPO + CTX: The median OS was 8.54 months (95% CI: 7.39, 19.71) in Dose Expansion cohort and 9.74 months (95% CI: 7.39, 27.89) in the pooled Dose Level 1 (DL1) and Dose Expansion cohort.

Phase 2

Event-Free Survival Based on Investigator Assessment (data cut-off 31 July 2023)

The first prespecified interim analysis leading to stop of enrolment was performed per protocol based on 33 EFS events (54 participants; 61.1%) with the data cut-off date 31 July 2023.

The study did not meet its primary objective of improving EFS with palbociclib + IRN + TMZ when compared to IRN + TMZ alone in the indicated participant population.

The median EFS was 1.5 months (95% CI: 1.4, 4.2) for the palbociclib + IRN + TMZ arm and 4.4 months (95% CI: 2.6, NE) for the IRN + TMZ arm (see Table 1).

The observed HR was 2.03 (95% CI: 0.902, 4.572; stratified 1-sided p-value=0.9621).

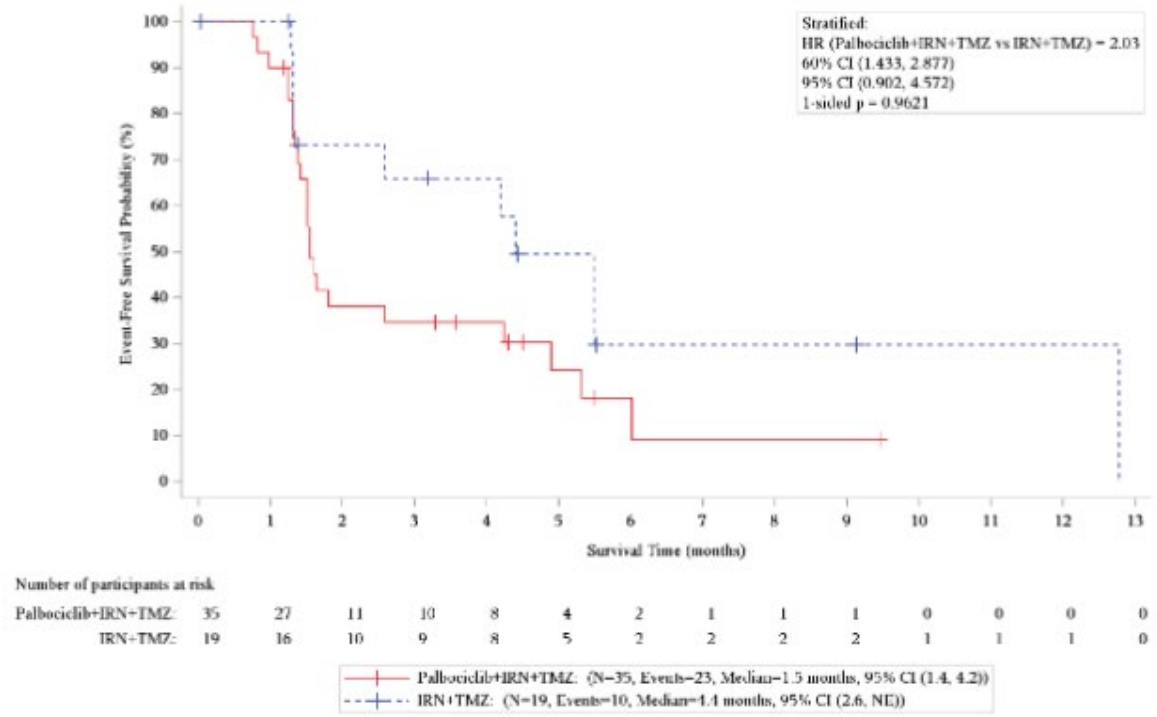
The Kaplan-Meier plot of EFS based on investigator assessment is presented in Figure 2.

Table 1 Summary of Event-Free Survival Based on Investigator Assessment (Phase 2) – Full Analysis Set

	Palbociclib+IRN+TMZ (N=35)	IRN+TMZ (N=19)
Participants with event, n (%)	23 (65.7)	10 (52.6)
Type of event, n (%)		
Progressive disease	22 (62.9)	10 (52.6)
Secondary malignancy	0	0
Death	1 (2.9)	0
Participants censored, n (%)	12 (34.3)	9 (47.4)
Reason for censoring, n (%)		
No adequate baseline assessment	2 (5.7)	0
Event after ≥ 2 missing or inadequate post-baseline assessments	1 (2.9)	0
Withdrawal of consent	1 (2.9)	0
Lost to follow-up	0	0
No adequate post-baseline tumor assessment	0	0
Ongoing without an event	8 (22.9)	9 (47.4)
EFS (%) (95% CI) [a]		
at 3 months	34.6 (18.3, 51.6)	66.0 (36.5, 84.3)
at 6 months	18.2 (5.4, 36.8)	29.7 (7.8, 56.0)
at 12 months	NE (NE, NE)	29.7 (7.8, 56.0)
at 18 months	NE (NE, NE)	NE (NE, NE)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [b]		
Q1	1.35 (1.25, 1.51)	1.31 (1.31, 5.49)
Median	1.54 (1.41, 4.24)	4.40 (2.60, NE)
Q3	4.90 (1.64, 6.01)	12.78 (4.40, NE)
Stratified analysis [c] Comparison vs IRN+TMZ		
Hazard Ratio [d]	2.03	
60% CI [d]	1.433, 2.877	
95% CI [d]	0.902, 4.572	
1-sided p-value [e]	0.9621	

The denominator to calculate percentages is N, the number of participants in the full analysis set within each treatment.
[a] Estimated from the Kaplan-Meier curve. CIs are derived using the log-log transformation with back transformation to untransformed scale.
[b] Based on the Brookmeyer and Crowley method.
[c] Stratified by type and time of current disease recurrence (primary refractory or 1st recurrence < 2 years versus 1st recurrence≥2 years or 2nd or greater recurrence) at randomization from IRT stratification values.
[d] Hazard ratio based on Cox proportional hazards model. Naïve CIs are presented.
[e] p-value based on stratified log-rank test.
PFIZER CONFIDENTIAL SDTM Creation: 30NOV2023 (14:03) Source Data: adtte Table Generation: 21FEB2024 (13:47)
(Data cutoff date : 31JUL2023 Database snapshot date : 21NOV2023) Output

Figure 2 Kaplan-Meier Plot of Event-Free Survival Based on Investigator Assessment (Phase 2)



Overall Survival (LPLV; data cut-off 06 August 2025)

Twenty-six (26) deaths (61.9%) were reported in the palbociclib arm, and 15 deaths (71.4%) were reported in the control arm.

The median OS was 10.68 months (95% CI: 8.44, 20.90) in the palbociclib arm and 11.43 months (95% CI: 7.46, 19.84) in the control arm.

The HR of palbociclib + IRN + TMZ arm vs. IRN + TMZ arm was 0.94 (95% CI: 0.49, 1.79).

TSC

Overall Survival (LPLV; data cu-toff 06 *August 2025*)

OS data was immature. Only 2 of 7 participants (28.6%) were reported dead.

2.3.2.6. Safety results

2.3.2.6.1. Exposure

Phase 1

For details on dose exposure in phase 1, refer to the 1st interim report assessed within the procedure EMEA/H/C/003853/P46/006. There are no further updates.

Phase 2

For details on dose exposure in phase 2, refer to the 2nd interim report assessed within the procedure EMA/PAM/0000250384 (P46) for details on dose exposure. There are no further updates.

TSC

As of LPLV (06 August 2025), the median duration of treatments for all participants was 1.8 months (range: 0.3, 24.0). The median relative dose intensity was 95.1% (range: 66.7%, 100.0%) for palbociclib, 96.9% (range: 66.7%, 100.0%) for TOPO, and 97.1% (range: 66.7%, 100.0%) for CTX.

2.3.2.6.2. Summary of adverse events

For more details, refer to the 1st and 2nd interim reports assessed within the procedures EMEA/H/C/003853/P46/006 and EMA/PAM/0000250384 (P46).

A short summary of the safety profile of treatment with palbociclib (75mg/m^2) in combination with TMZ + IRN in paediatric Ewing sarcoma patients is presented below. These data are the final data from the phase 2 part of the study, however, the only data that have been updated since the previous 2nd interim report are the data on fatal TEAEs.

As of the data cut-off date (26 August 2024), all treated 62 participants in the phase 2 part of the study were evaluable for TEAEs. Most participants experienced at least 1 all-causality TEAE: 38 of 41 participants (92.7%) in the palbociclib arm and 20 of 21 participants (95.2%) in the control arm.

The most common (reported in ≥20% participants) TEAEs in the palbociclib arm and control arm, respectively, were Neutropenia (65.9% versus 42.9%), Vomiting (36.6% versus 23.8%), Leukopenia (31.7% versus 28.6%), Diarrhoea (31.7% versus 42.9%), Anaemia (29.3% versus 28.6%), Nausea (26.8% versus 19.0%) and Thrombocytopenia (24.4% versus 28.6%).

The incidence of participants with TEAEs Grade 3-4 were similar between the palbociclib arm and the control arm (82.9% versus 81.0%).

The incidence of participants who had SAEs in the palbociclib arm was higher than the control arm (all causality SAEs 36.6% versus 19.0%; treatment-related SAEs 17.1% versus 14.3%).

The most common SAEs reported in >1 participant were Infections (14.6% versus 4.8%), and Febrile neutropenia (9.8% versus none). The term "Infections" is a cluster term and comprises of all PTs under SOC Infections and Infestations).

The incidence of participants with TEAEs leading to permanent treatment discontinuation was low, 2 participants in each treatment arm (4.9% versus 9.5%). Three events leading to permanent treatment discontinuation were considered treatment-related, 1 event in the palbociclib arm (Grade 3 AST/ALT elevations) and two events in the control arm (Grade 3 ALT, Grade 3 Diarrhoea). The incidence of participants with TEAEs leading to dose reduction of any study treatments was also low, 1participant in the palbociclib arm and 4 participants in the control arm (2.4% versus 19.0%). The TEAEs leading to dose reductions were Diarrhoea, Nausea, and Vomiting, and Thrombocytopenia, all of which were assessed as treatment related.

In contrast, the incidence of participants with TEAEs leading to temporary dose interruptions of any study drug was higher in the palbociclib arm than in the control arm (61.0% versus 47.6%). The most common reasons for interruption were Neutropenia and Thrombocytopenia in both treatment arms.

As of the data cutoff date (26 August 2024), one fatal TEAE (Grade 5) had occurred in the palbociclib arm within 35 days after last dose of study treatments and the reason was underlying disease (neoplasm progression) and unrelated to treatment. No deaths were reported in the control arm.

During the follow-up period (beyond 35 days after last dose), a total of 36 deaths (58.1%) were reported including 23 deaths (56.1%) in the palbociclib arm and 13 deaths (61.9%) in the control arm. The primary cause of death was disease under study in both treatment arms.

2.3.3. Discussion on clinical aspects

Non-clinical data have indicated that the addition of a CDK4/6 inhibitor to a combination of a topoisomerase inhibitor and an alkylating agent may improve tumour growth inhibition in Ewing sarcoma (EWS) tumour models. The agreed PIP P/0117/2022 for palbociclib therefore includes evaluation of palbociclib in the treatment of paediatric EWS.

The primary analysis of the results of the randomised phase 2 part of study A5481092 (assessed within the procedure EMEA/H/C/003853/P46/006) did not show an improved EFS by adding palbociclib to the combination of IRN and TMZ in the treatment of paediatric r/r EWS, and the enrolment to the phase 2 part was stopped prematurely for lack of efficacy. The updated EFS and OS data submitted after the primary analysis does not alter the previous conclusions. The final OS data (LPLV) was 10.68 months (95% CI: 8.44, 20.90) in the palbociclib arm and 11.43 months (95% CI: 7.46, 19.84) in the control arm. The HR of palbociclib + IRN + TMZ arm vs. IRN + TMZ arm was 0.94 (95% CI: 0.49, 1.79).

Additionally, the Stage 1 neuroblastoma (NB) tumour-specific data with ineffective treatment of palbociclib + TOPO + CTX, submitted with the final clinical study report (LPLV), does not support a favourable benefit/risk profile in this patient population, although the low number of participants in the NSC (n=7) precluded definite conclusions.

The safety profile for the combination of palbociclib and IRN+TMZ in the paediatric EWS and NB population aligned with the known safety profiles of palbociclib, IRN and TMZ, respectively. As expected, palbociclib's mechanism of inhibiting cell proliferation, including a negative effect on haematopoiesis, led to a higher incidence of haematological toxicity, primarily asymptomatic Neutropenia. This increased risk of haematological toxicity resulted in an imbalance in the frequency of participants experiencing serious Infections (14.6% versus 4.8% in the palbociclib and control arm, respectively) and serious Febrile neutropenia (9.8% versus none in the palbociclib and control arm, respectively). Although the combination of palbociclib and IRN+TMZ in the paediatric EWS patients showed poor tolerability, with a high rate of temporary dose interruptions for palbociclib, no new safety signals were identified.

The SmPC was recently updated with paediatric data from all measures within the PIP P/0117/2022, within the procedure EMEA/H/C/003853/II/0045.

3. CHMP’s overall conclusion and recommendation

The final data from study A5481092 does not support a positive benefit risk for the addition of palbociclib to the combination of irinotecan and temozolomide in the treatment of paediatric Ewing sarcoma or neuroblastoma.

☒ **Fulfilled:**

In view of the available data regarding study A5481092, the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and ***no later than 60 days after the receipt*** of these conclusions.

The final data from study A5481092 warrant an update of the SmPC.

The MAH is requested to update the SmPC with the final OS data from the study and to provide a brief description of the results from the Tumour Specific Cohort (TSC) on neuroblastoma patients, i.e., the cohort was not pursued because the prespecified requirements were not met and enrolment was stopped. The MAH must submit a type II variation application for approval of these SmPC updates.